A Dissertation on

A STUDY ON PREVALENCE OF HYPERHOMOCYSTEINEMIA AND ITS CORRELATION WITH CAROTID INTIMA MEDIA THICKNESS IN ISCHEMIC STROKE PATIENTS.

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001

APRIL 2015

CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. APPUNNI .S,** Post - Graduate Student (May 2012 TO April 2015) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**A STUDY ON PREVALENCE OF HYPERHOMOCYSTEINEMIA AND ITS CORRELATION WITH CAROTID INTIMA MEDIA THICKNESS IN ISCHEMIC STROKE PATIENTS"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2015.

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CERTIFICATE BY THE GUIDE

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CHENNAI – 600001.

DECLARATION

I, **Dr. APPUNNI. S,** declare that I carried out this work on "**A STUDY ON PREVALENCE OF HYPERHOMOCYSTEINEMIA AND ITS CORRELATION WITH CAROTID INTIMA MEDIA THICKNESS IN ISCHEMIC STROKE PATIENTS"** in the Medical wards of Government Stanley Hospital during the period November 2013 to September 2014. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

DR. APPUNNI .S

ACKNOWLEDGEMENT

At the outset I thank our dean **DR.A.L. MEENAKSHI SUNDARAM M.D., D.A,** for permitting me to carry out this study in our hospital.

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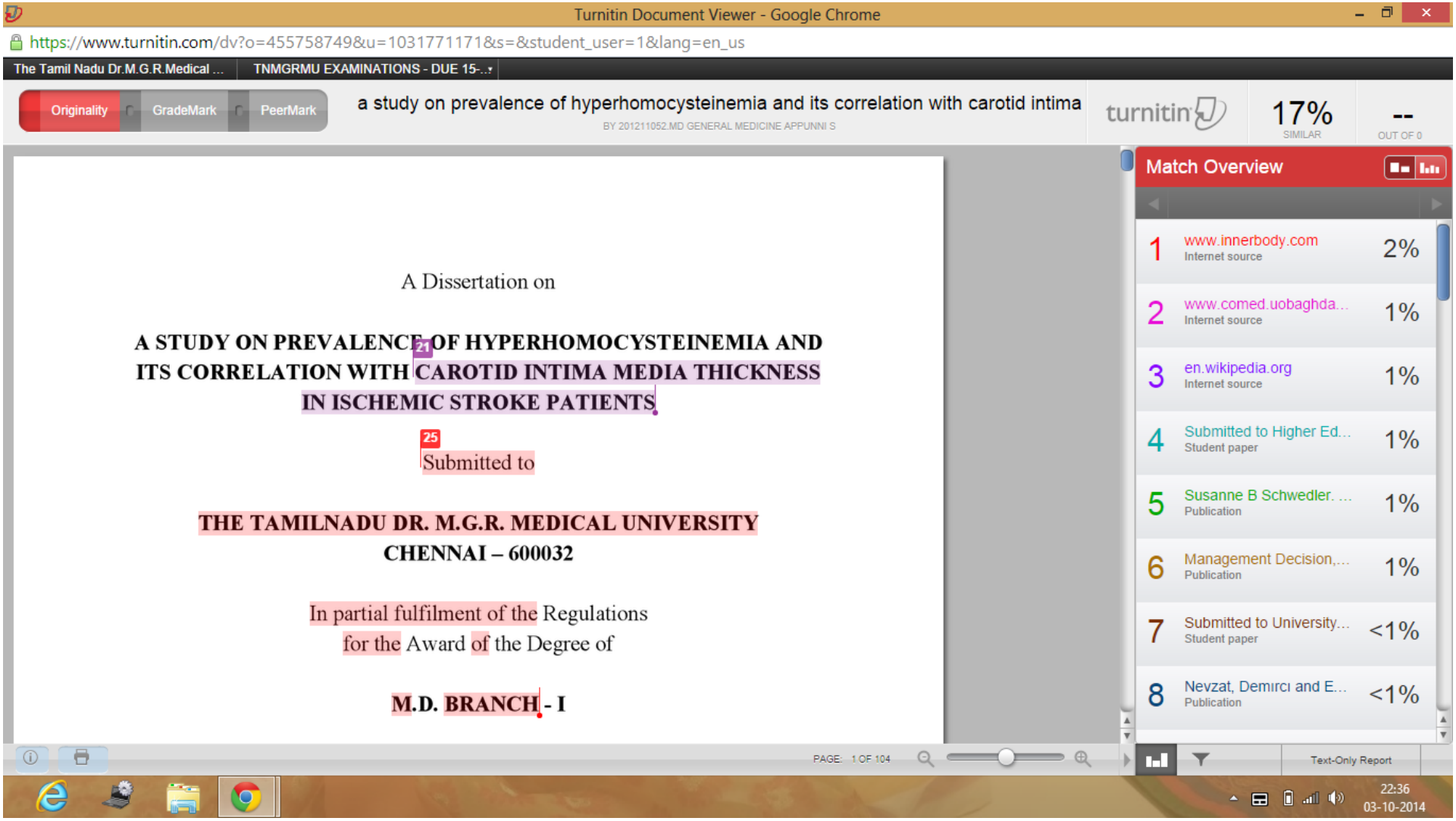
I thank all my colleagues, House Surgeons, and Staff nurses and other para medical workers for their support.

Last but not the least; I sincerely thank all those **patients** who participated in this study, for their co-operation.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INTRODUCTION

Ischemic stroke is one of the common diseases found in medical wards, and is one of the common causes of morbidity and mortality worldwide. There are many causes of ischemic stroke and hyperhomocysteinemia is one of the documented causes. Homocysteine is synthesised in our body from methionine in a multistep process. Many vitamins like folic acid, vit B12, pyridoxine are involved in the homocysteine biosynthesis. Hyperhomocysteinemia is a proatherosclerotic state which is due to many pathological mechanisms. Homocysteine more than 15 µmol/L is taken as hyperhomocysteinemia. It has also been implicated in various other diseases like cardiovascular diseases, neuropsychiatric disorders, pregnancy complications, etc. There are many causes for hyperhomocysteinemia of which nutritional deficiencies and genetic causes are the most common. Treatment of hyperhomocysteinemia mainly involes nutritional supplementation with folic acid and Vit.B12, and others.

Carotid intima media thickness (CIMT)measurement is accepted as a method to identify atherosclerosis, as increased CIMT has been found to be associated with increased cardiovascular and cerebrovascular complications. It is measured routinely by B-mode USG. CIMT has been found to be increased in hyperhomocysteinemia as well.

AIMS AND OBJECTIVES

1. To study the clinical profile of ischemic stroke at Government Stanley Hospital, Chennai.

2. To study prevalence of hyperhomocysteinemia in these patients and correlate with carotid intima media thickness in these patients.

MATERIALS AND METHODS

Place of study:

Department of general medicine, medical OPD and medical wards, Stanley medical college and hospital, Chennai.

Duration:

November 2013 to September 2014.

Study design:

Prospective observational study

Patient selection:

Any patient with ischemic stroke in medical OPD and medical wards.

Sample size :

75 patients

Ethical committee approval

Ethical committee approval was obtained for the study

Methodology

Patients admitted with symptoms suggestive of ischemic stroke, which is proved later by CT brain, will undergo serum homocysteine measurements and carotid USG to measure carotid intima media thickness. The study will be aimed at observing the prevalence of hyperhomocysteinemia in ischemic stroke and also whether there is any correlation between the serum homocysteine levels and carotid intima media thickness.

Exclusion criteria:

Hemorrhagic stroke, patients on folic acid supplements, patients on anti-epileptics/ OCPs/ drugs causing hyperhomocysteinemia, chronic kidney disease, pre-existing coronary artery disease

Stastical analysis

Data will be analysed with SPSS software version 16.0 for windows.

All continuous data will be expressed as mean and sd and will be analysed using students t test.

Categorical data will be expressed as number (percentage) and analysed by chi square or fishers exact test.

Pearson's correlation coefficient and linear regression analysis will be undertaken to establish correlation and regression among variables.

P value of <0.05 was considered as statistically significant

CONSENT

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up for this study after getting a written / informed consent from these patients or their relatives in the local vernacular language.

STUDY SUBJECTS

All the patients who fulfilled the inclusion criteria were included in this study. The included patients were subjected to detailed history taking, complete physical examination and the relevant laboratory investigations as per a proforma, exclusively designed for the study.

I. INTRODUCTION

Ischemic stroke is one of the common diseases found in medical wards, and is one of the common causes of morbidity and mortality worldwide. There are many causes of ischemic stroke and hyperhomocysteinemia is one of the documented causes. Homocysteine is synthesised in our body from methionine in a multistep process. Many vitamins like folic acid, vit B12, pyridoxine are involved in the homocysteine biosynthesis. Hyperhomocysteinemia is a proatherosclerotic state which is due to many pathological mechanisms. Homocysteine more than 15 µmol/L is taken as hyperhomocysteinemia. It has also been implicated in various other diseases like cardiovascular diseases, neuropsychiatric disorders, pregnancy complications, etc. There are many causes for hyperhomocysteinemia of which nutritional deficiencies and genetic causes are the most common. Treatment of hyperhomocysteinemia mainly involes nutritional supplementation with folic acid and Vit.B12, and others.

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II. REVIEW OF LITERATURE

HOMOCYSTEINE

Homocysteine is a sulphur containing amino acid and each molecule of homocysteine contains one atom of sulphur.

It is a homologue of cysteine and it differs from cysteine by an additional methylene bridge (-CH2-).

Homocysteine is synthesised from methionine by the removal of its terminal methyl group.

Elevated levels of homocysteine in the blood, called hyperhomocysteinemia, has been implicated in the pathogenesis of many diseases like cardiovascular disease, stroke, pregnancy problems, osteoporosis, Alzheimer's, schizophrenia and others.

HISTORY

Butz and du Vigneaud discovered homocysteine in 1932. They heated methionine in sulphuric acid and incidentally produced homocysteine as a result.

Dr. Kilmer McCully came up with the hypothesis in mid 1960s that moderate elevations of homocysteine can lead to strokes and heart attacks. But this theory was not accepted then.

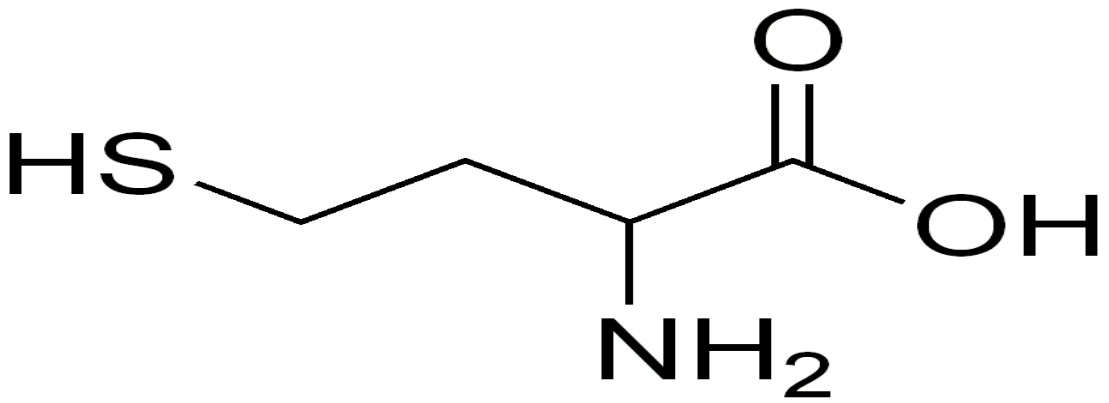
Later, in mid 90s, by the work of Dr. Meir Stampfer, researchers accepted that homocysteine was an independent risk factor for strokes and cardiovascular disease.

BIOCHEMISTRY

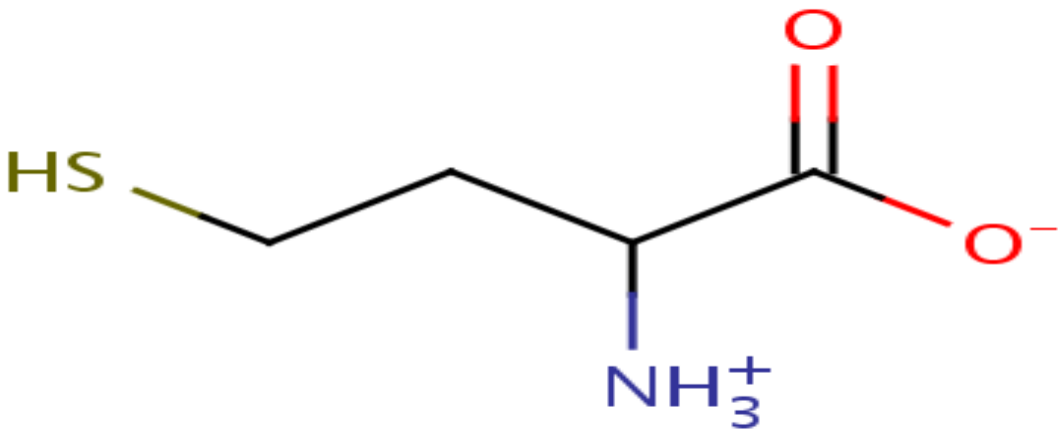
Molecular formula - $C_4H_9NO_2S$

Chemical nomenclature - 2-Amino-4-sulfanylbutanoic acid

Molar mass – 135.18 mg/mol



At neutral pH values, homocysteine exists as a zwitterion or a dipolar ion

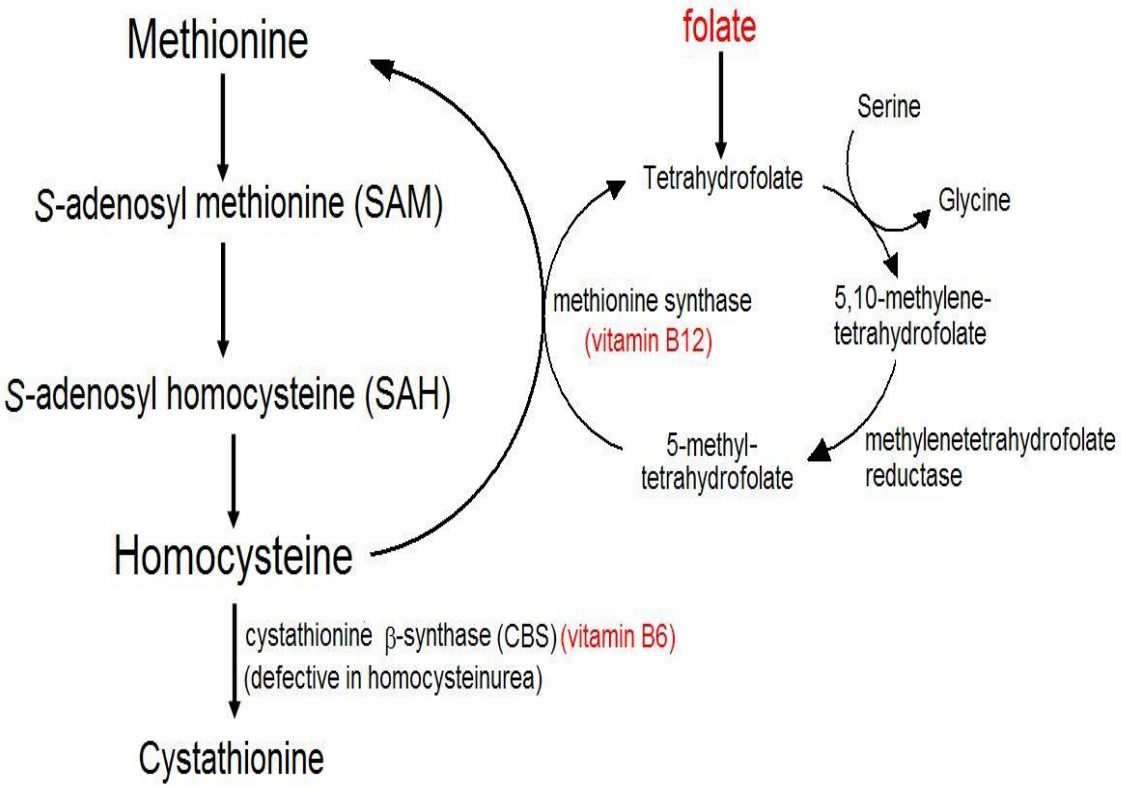


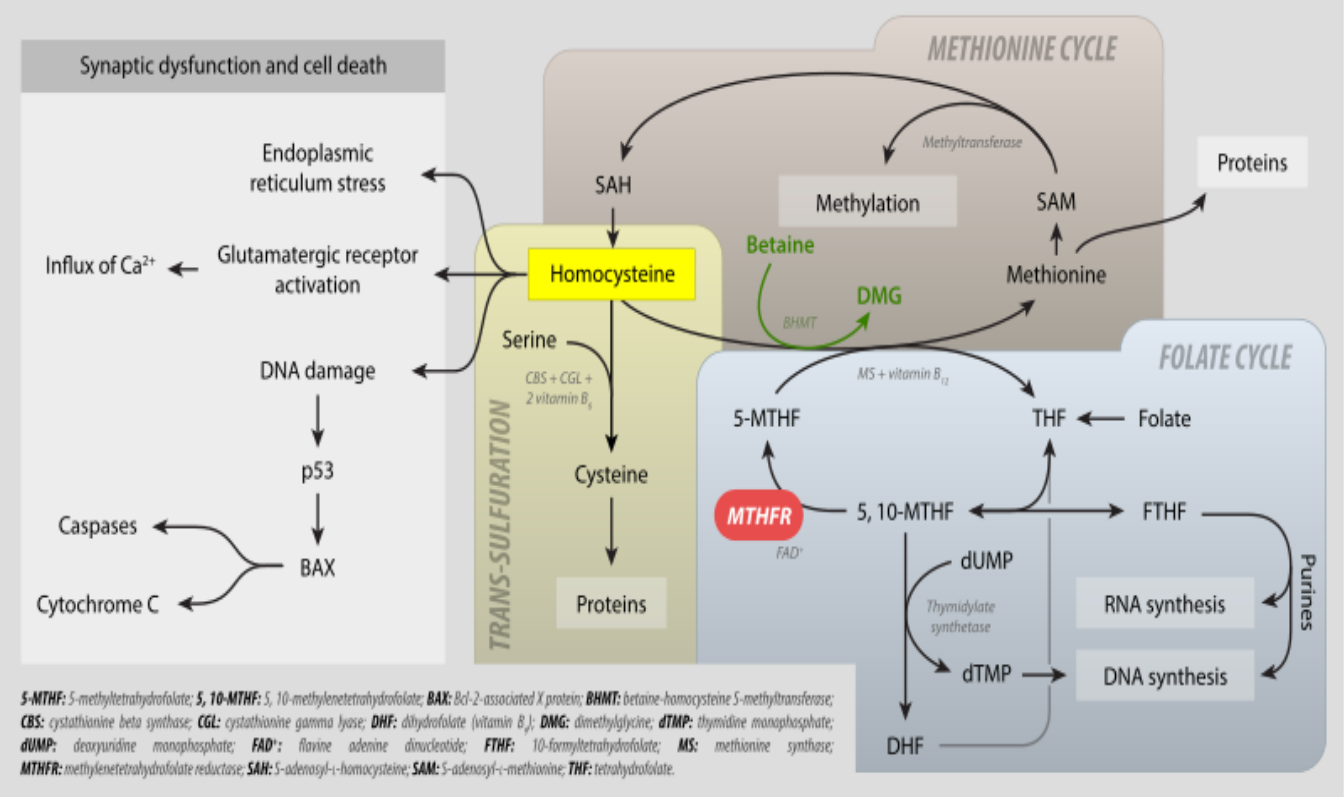
BIOSYNTHESIS

Homocysteine is not available from the diet. It is synthesised in the body from methionine via a multi-step process.

1. Methionine initially gets an adenosine group from ATP and this reaction is catalysed by the enzyme S-adenosyl methionine synthetase, to form S-adenosyl methionine (SAM)

2. The methyl group of SAM is then transferres to an acceptor molecule, to form S-adenosyl homocysteine.
3. Then hydrolysis of the adenosine yields Homocysteine





Homocysteine thus formed can enter 2 pathways :

1. Cysteine biosynthesis via Transsulfuration – homocysteine is condensed with serine by the enzyme cystathione β synthase to form cystathionine. Pyridoxine is needed as a co-factor for this reaction. Cystathionine is then converted into cysteine by cystathionine γ lyase. Ammonia and alpha-keto glutarate are also formed along with cysteine.
2. Methionine salvage – homocysteine is converted back into methionine by the enzyme Methionine synthase. This enzyme needs N5 methyl tetrahydrofolate as methyl donor and vitamin B12.

Other minor roles –

- Homocysteine can also form homocysteine thiolactone
- Homocysteine is an allosteric antagonist at dopamine receptors (D2)

So, vitamins B6,B12 and folate are essential for metabolism of homocysteine. If a person ingests a protein rich food and his diet is deficient in these vitamins, his homocysteine levels in the blood will rise and can cause hyperhomocysteinemia , which in turn can lead to further complications.

HYPERHOMOCYSTEINEMIA

Abnormal levels of homocysteine in serum more than 15 µmol/L is defined as hyperhomocysteinemia

It can be further classified as :

- Mild hyperhomocysteinemia - 15 – 30 µmol/L
- Moderate hyperhomocysteinemia - 30 – 100 µmol/L
- Severe hyperhomocysteinemia - >100 µmol/L

Hyperhomocysteinemia has been implicated in the pathogenesis of various diseases like myocardial infarction, stroke, osteoporosis, neuropsychiatric disorders, alzheimers, pregnancy complications and many other diseases.

There are many diseases, drugs and other factors which can lead to an increased level of homocysteine in the blood.

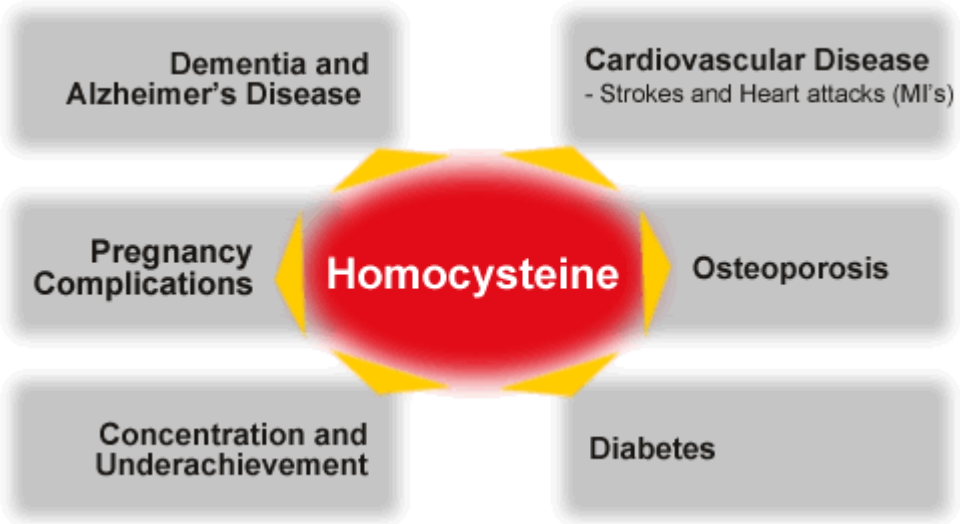
Genetic mutations to various enzymes involved in metabolism or synthesis of homocysteine will also lead to hyperhomocysteinemia.

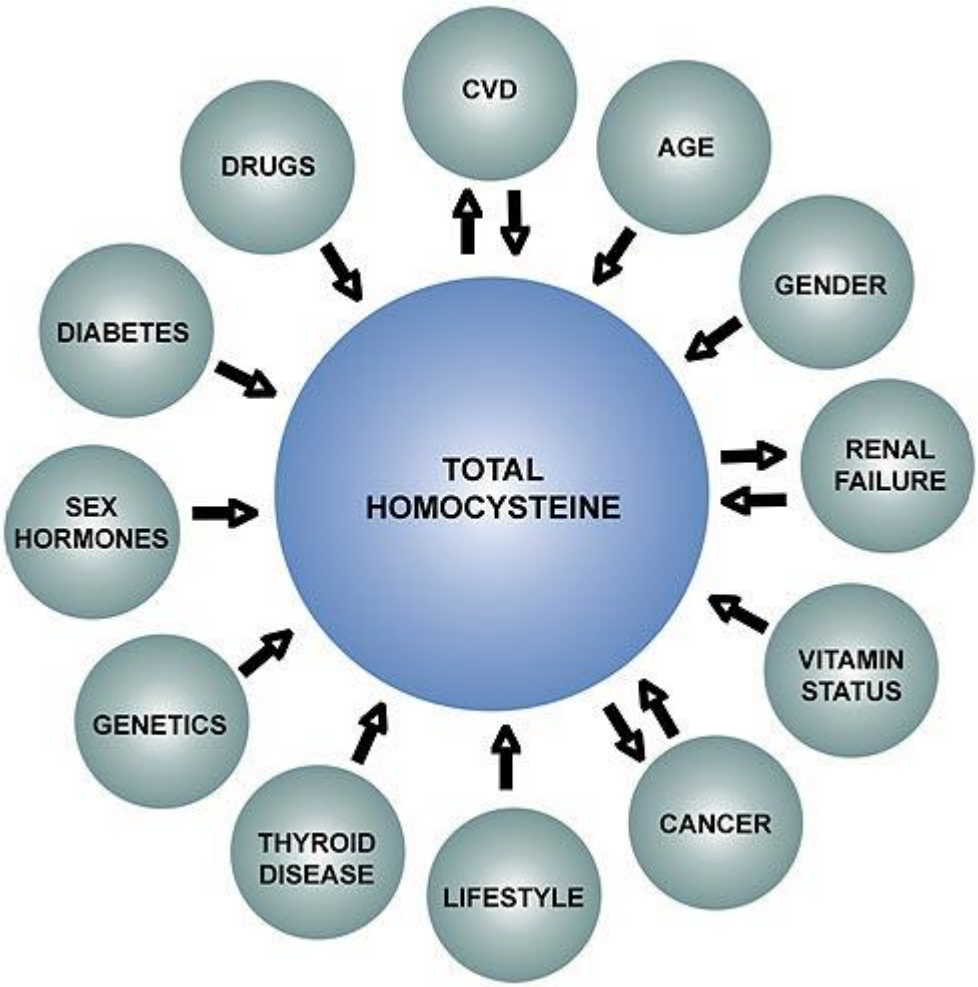
Vitamin deficiencies (folate, vitamin B12, pyridoxine) are one of the common causes of this condition.

Old age, male gender, smoking and alcoholism are also related to increasing homocysteine levels in blood.

Other conditions including various medical disorders like chronic kidney disease, psoriasis and SLE also are implicated for hyperhomocysteinemia.

Drugs like antiepileptics (phenytoin, carbamazepine), methotrexate, nicotinic acid, etc are also common causes of hyperhomocysteinemia.


Dementia and Alzheimer's Disease
Cardiovascular Disease
- Strokes and Heart attacks (MI's)
Pregnancy Complications
Homocysteine
Osteoporosis
Concentration and Underachievement
Diabetes


CVD
DRUGS
AGE
GENDER
DIABETES
TOTAL HOMOCYSTEINE
RENAL FAILURE
SEX HORMONES
VITAMIN STATUS
GENETICS
CANCER
THYROID DISEASE
LIFESTYLE

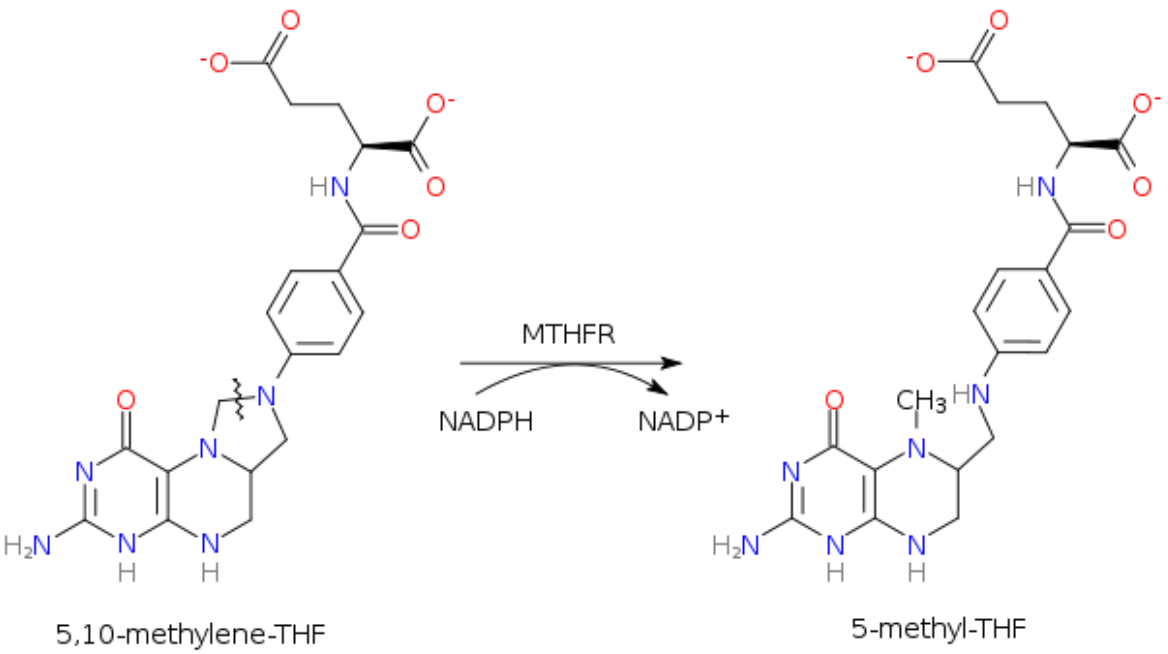
CAUSES OF HYPERHOMOCYSTEINEMIA :

- Enzyme deficiencies
  - Cystathionine β-synthase
  - Methionine synthase
  - 5-Methyltetrahydrofolate reductase
- Vitamin deficiencies
  - Folate
  - Vitamin B_6
  - Vitamin B_{12}
- Demographics
  - Increasing age
  - Men
  - Tobacco use
  - Solid organ transplant recipients
- Chronic medical disorders
  - Renal dysfunction
  - Systemic lupus erythematosus
  - Malignant neoplasm
  - Psoriasis
- Acute-phase response to systemic illness
- Medication use
  - Methotrexate
  - Nitrous oxide
  - Antiseizure agents (phenytoin and carbamazepine)
  - Nicotinic acid
  - Colestipol
  - Thiazide diuretics

GENETIC CAUSES :

Most common genetic cause of hyperhomocysteinemia is a 5-Methyltetrahydrofolate reductase (MTHFR) defect. 9-17% of the population is homozygous for this mutant enzyme whereas heterozygosity is seen in 30-41% of the general population.

The MTHFR gene is on chromosome 1 (1p36.3) and the 2 most common studied mutations are the C677T and A1298C single nucleotide polymorphisms (SNP).



Homozygous deficiencies of cystathionine β synthase causes homocystinuria , which is characterised by mental retardation, premature atherosclerosis and venous & arterial thrombosis.

These patients will have severe hyperhomocysteinemia with serum homocysteine levels more than 300 µmol/L.

Heterozygous deficiency of this enzyme is more common than homozygous, and it causes moderate hyperhomocysteinemia.

Diminished activity of methionine synthase will also cause hyperhomocysteinemia, and this condition is associated with birth defects, blindness and neurological symptoms.

VITAMIN DEFICIENCIES :

Folic acid, vitamin B12 and pyridoxine act as cofactors or cosubstrates in various enzymatic reactions in homocysteine biosynthesis and metabolism. So patients with low levels of folate and vit. B12 , hyperhomocysteinemia has been detected.

OTHER CAUSES :

Homocysteine levels in blood increase with increasing age.

Males have been found to have higher homocysteine levels when compared to their female counterparts.

Tobacco use, smoking and alcoholism also increase blood homocysteine levels.

Homocysteine levels were found to be elevated in patients with chronic kidney disease, SLE, deep vein thrombosis, solid organ transplantation and psoriasis.

Many commonly used drugs like phenytoin, carbamazepine, methotrexate, nicotinic acid, thiazides, nitrous oxide and colestipol also increase blood homocysteine levels.

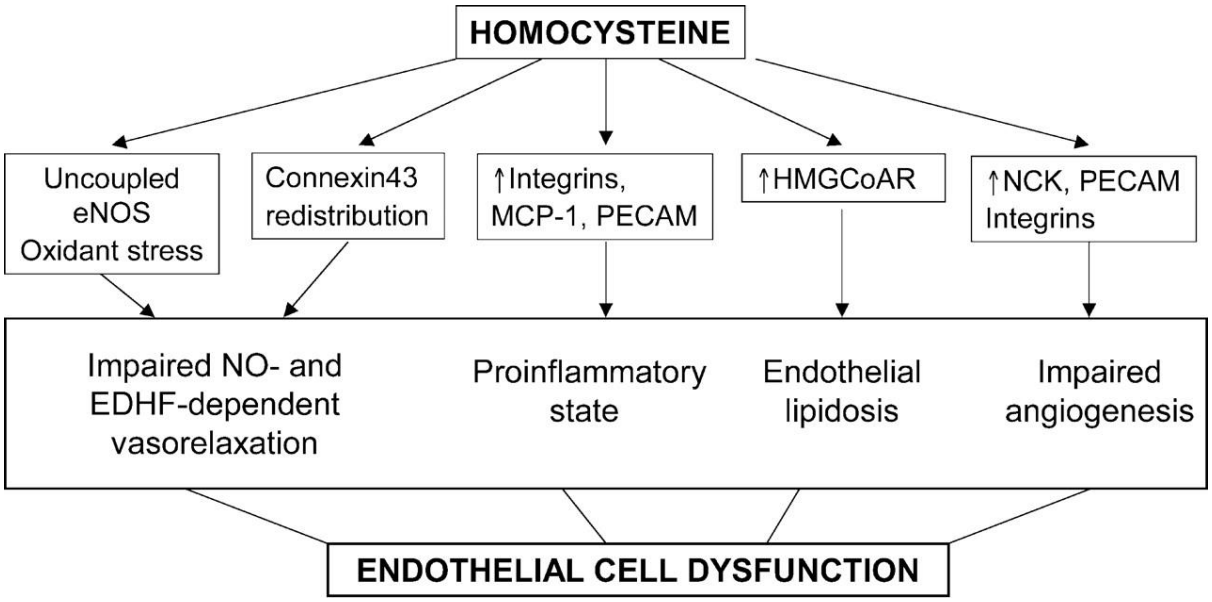
It has also been found to get elevated during an acute phase of a systemic illness.

PATHOPHYSIOLOGY AND PATHOGENESIS

Hyperhomocysteinemia causes various vascular and haematological abnormalities which lead to the formation of a prothrombotic and proatherogenic metabolic milieu.

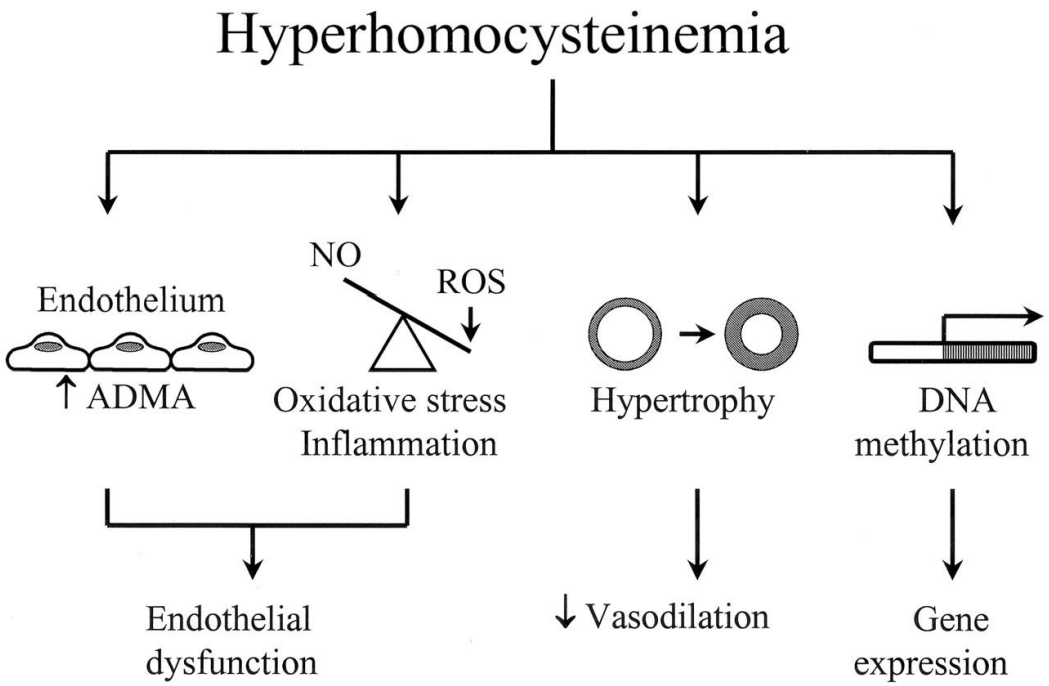
The various abnormalities seen are –

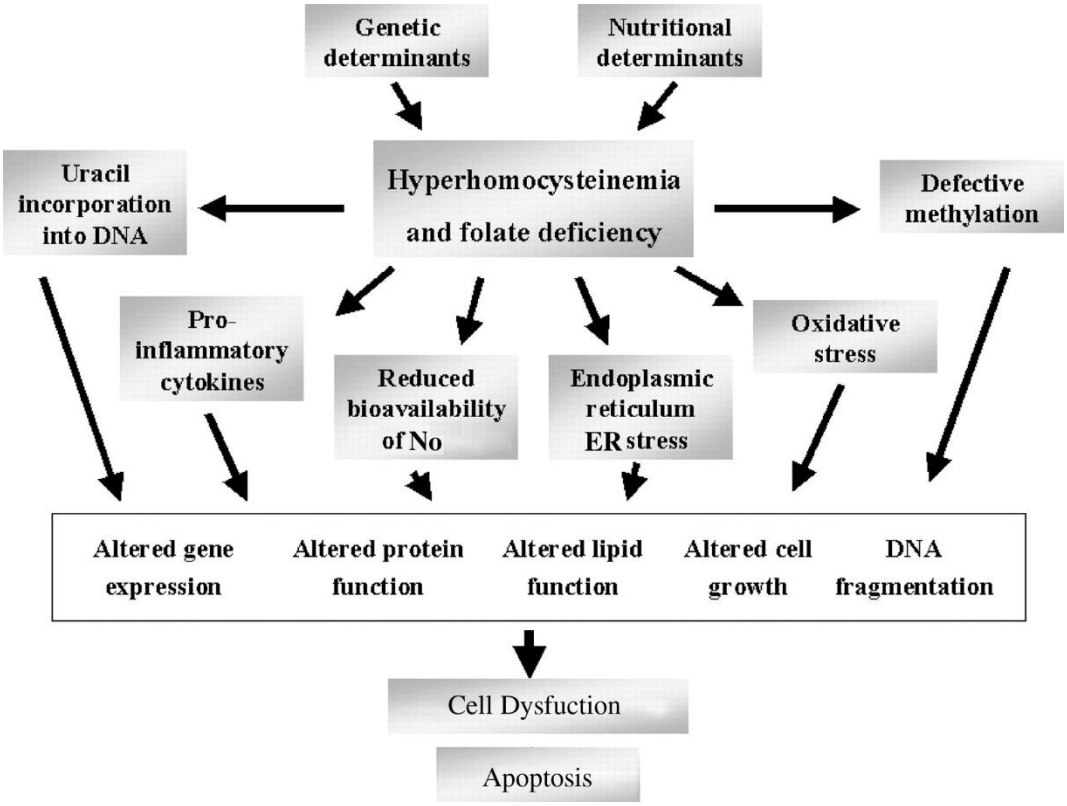
1. Endothelial cell injury – it is the first step in the initiation of atherosclerosis. It is manifested as – a) impaired NO and EDHF dependent vasodilation, b) decreased activity of tissue type plasminogen activator, c) endothelial lipidosis and d) increased smooth muscle proliferation.

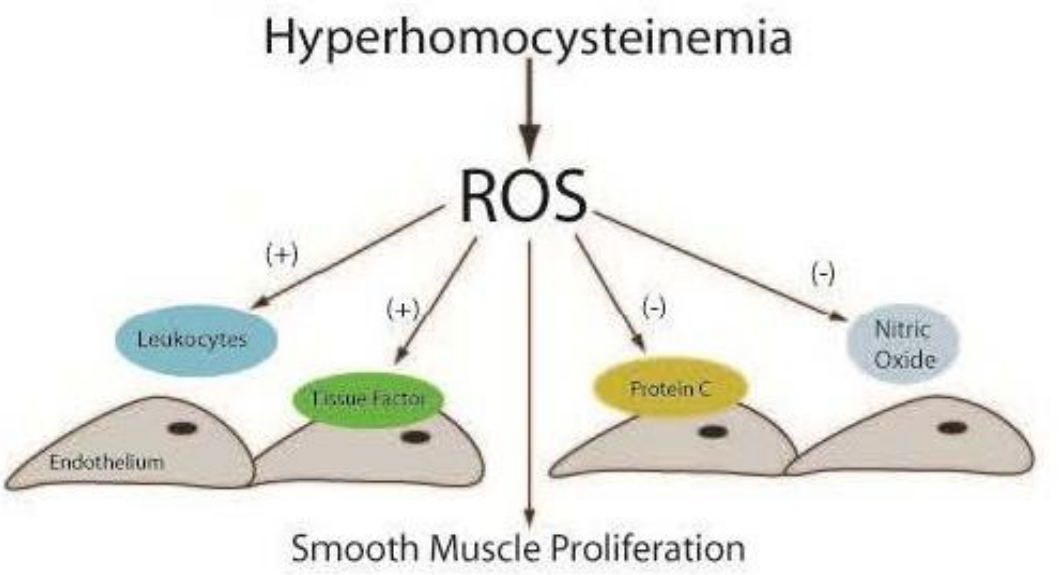


2. Clotting cascade abnormalities – a) inhibition of natural anticoagulants like factor C and antithrombin III, b) activation of factors V, X and XII
3. Homocysteine increases binding of lipoprotein a to fibrin, which stimulates the smooth muscle cell proliferation.
4. Homocysteine levels are related to the serum fibrinogen levels, which in itself is also a separate risk factor for atherosclerosis.

5. Increased platelet aggregation - due to increased thromboxane A2 synthesis and decreased prostacyclin production
6. Homocysteine decreases release of nitric oxide
7. It also produces reactive oxygen species which also cause endothelial dysfunction.




Genetic determinants
Nutritional determinants
Hyperhomocysteinemia and folate deficiency
Uracil incorporation into DNA
Defective methylation
Pro-inflammatory cytokines
Reduced bioavailability of No
Endoplasmic reticulum ER stress
Oxidative stress
Altered gene expression
Altered protein function
Altered lipid function
Altered cell growth
DNA fragmentation
Cell Dysfuction
Apoptosis


Hyperhomocysteinemia
ROS
(+)
(+)
(-)
(-)
Leukocytes
Tissue Factor
Protein C
Nitric Oxide
Endothelium
Smooth Muscle Proliferation

PATHOPHYSIOLOGICAL FINDINGS

- Endothelial cell injury
  - Impaired endothelium-dependent vasodilation
  - Impaired endogenous tissue-type plasminogen activator activity
  - Increased smooth muscle proliferation
- Increased platelet aggregation
  - Increased synthesis of thromboxane A_2
  - Decreased synthesis of prostacyclin
- Abnormalities of the fibrinolysis
  - Activation of factors V, X, and XII
  - Inhibition of antithrombin III and factor C
  - Enhanced lipoprotein(a) binding to fibrin
- Correlation with fibrinogen levels

It has also been postulated that hyperhomocysteinemia exerts its pathogenic effects due to a molecule - S-adenosyl-L-homocysteine (SAH), which gets accumulated .

SAH is a strong noncompetitive inhibitor of COMT (catechol-O-methyl transferase). COMT is involved in the metabolism of various catechol substrates like catecholamines and catechol estrogens.

This will result in increase in blood / tissue levels of catecholamines.

The vasculature is thus exposed to large levels of these catecholamines. Hence the vascular endothelial cells undergo chronic cumulative damage caused by the excess oxidative products produced by the catecholamines.

This explains why hyperhomocysteinemia is an increased risk actor for cardiovascular as well as neurodegenerative diseases.

Excess homocysteine can also be converted into homocysteine thiolactone, which is a highly reactive intermediate which thiolates free aminogroups in LDL and cause them to aggregate and get endocytosed by macrophages. These lipid deposits form atheromas.

Homocysteine can also react with lysyl aldehyde groups on collagen and block them, and binds to fibrillin 1, causing Marfan like symptoms.

EPIDEMIOLOGY IN INDIA :

When compared to the west, Indian studies which examined the prevalence of hyperhomocysteinemia in the Indian community have reported a much higher incidence in the range of 52 to 84%. The mean homocysteine levels are also quiet high, ranging from 19.5 to 23.2 µmol/L.

In India, marked hyperhomocysteinemia has been observed with markedly decreased intake of vitamin B12 and folic acid in the vegetarians and urban middle class people.

Low plasma concentrations of folate, vitamins B-6 and B-12,male gender, older age, and urban life were all independently associated with elevated homocysteine levels, with low folate as the strongest determinant.

Although majority of Indians are vegetarian, there is also a high incidence of folate deficiency reported. The reason for this has been found that Indians usually cook their food for longer duration, which can destroy nearly 90% of the folic acid.

Pyridoxine deficiency has been found to be quite common among Indians.

Another factor that predisposes Indians to hyperhomocysteinemia is the genetic defect in the enzymes that metabolize homocysteine.

Many studies have found that nearly one-third of Indians have a genetic defect which leads to decreased activity of MTHFR.

There are two polymorphisms of the MTHFR enzyme which are common amongst Indians, they are the C677T and A1298C polymorphisms.

In a study, the presence of either of the polymorphisms was examined, and they found that 43.5% of the population had decreased MTHFR activity.

However, compared to diet ,the effect of genetic factors in increasing the homocysteine level seemed to be modest.

LAB MEASUREMENT OF HOMOCYSTEINE

Physiologically, homocysteine exists as oxidised, reduced and protein bound forms. The initial methods introduced in mid 80s resolved these problems (presence of multiple homocysteine forms in the plasma) by converting all the species into the reduced form, which was an indicator of total homocysteine.

Later, modern methods used pretreatment of plasma specimens with reducing agents like dithiothreitol, dithioerythritol, mercaptoethanol, tributylphosphine or tris(2 carboxylethyl) phosphine which converted all the homocysteine species into the reduced form.

Modern total homocysteine measurement methods include enzyme immunoassays and chromatography based methods.

Immunoassays are the most commonly used technique for routine purposes.

Most of the research studies have measured Homocysteine levels using high-performance liquid chromatography (HPLC).

In HPLC, Homocysteine can be seen as a fluorescent derivative. Electrochemical detection of homocysteine is also possible.

Competitive immunoassays for Homocysteine have been developed, on a variety of instruments in the clinical laboratory. These are also now available in many labs nowadays.

These assays have been based on the quantitative enzymatic conversion of Homocysteine to the molecule S-adenosyl homocysteine (SAH).

Many antibodies have been produced that specifically recognize this compound, therefore competitive assay of the concentration of S-adenosylhomocysteine was easily measured.

Recent development of simple calorimetric enzyme assays for Homocysteine has allowed analyses to be performed on routine clinical biochemistry analyzers.

These assays are based on either on enzymatic release of hydrogen sulfide which reacts to form a chromogen or an enzymatic cycling assay.

Tandem mass spectrometry is another option for analysis of Homocysteine.

Method comparisons showed that there were relatively small variations between different methods. Hence all methods offer sufficient analytical performance for routine clinical use; therefore ,choice of method usually will be based on practical considerations of efficiency,cost and labour, and on which analyzers are available in the laboratory.

Blood samples have to be taken in test tubes containing an anticoagulant like EDTA and should be centrifuged as early as possible,before 30 minutes, to avoid false positive homocysteine values, as it can be released from red blood cells.

Some patients may have abnormal homocysteine metabolism . Because of this problem, these patients may have normal fasting plasma homocysteine levels, a flase negative test, and hence they require a provocative testing – called methionine loading test - to bring out this problem.

Methionine loading test – administer 100 mg/kg of methionine orally, later, after around 6-8 hours, measure the plasma homocysteine levels.

According to various studies, it has been shown that the methionine loading test identifies nearly an additional 27% of hyperhomocysteinemia cases.

But since this methionine loading test is costly and time consuming, and also since there is inter individual variation in the time needed for peak homocysteine levels, the role of this test in routine clinical practice is

controversial. And most of the studies based on hyperhomocysteinemia and atherosclerotic vascular disease measured only the fasting plasma homocysteine levels. So the methionine loading test may be done once its efficacy is proved without doubt.

SCREENING FOR HYPERHOMOCYSTEINEMIA

Screening for hyperhomocysteinemia may be advised for those people who are at high risk for developing premature atherosclerotic vascular disease and those persons who are having risk factors for developing hyperhomocysteinemia.

These patients include those with :

(1) atherosclerotic vascular disease patients without conventional risk factors

(2) premature atherosclerotic vascular disease (ie.before 60 years of age)

(3) premature atherosclerotic vascular disease in a first-degree relative

(4) atherosclerotic vascular disease risk factors related to hyperhomocysteinemia, like smoking, hypertension ,old age ,etc

(5) chronic renal failure patients

(6) systemic lupus erythematosus

(7) unexplained deep venous thrombosis

(8) solid organ transplantation

(9) severe psoriasis

(10) prolonged use of medications causing hyperhomocysteinemia

TREATMENT OF HYPERHOMOCYSTEINEMIA

Dietary and lifestyle modifications :

1. Avoid methionine rich foods like dairy products and red meat
2. Exercise
3. Stop alcohol, smoking and coffee
4. Weight loss
5. Avoid drugs causing hyperhomocysteinemia

Drug therapy :

1. Vitamin supplementation – folic acid, vit.B12, vit.B6
2. N-acetyl cysteine
3. Omega 3 PUFAs
4. Taurine supplementation

5. Trimethylglycine and choline supplementation

6. S-adenosyl-L-methionine supplementation

7. Riboflavin supplementation

VITAMIN SUPPLEMENTATION :

Treatment with folic acid of doses 400 µg or more daily has been found to lower homocysteine levels by 30% to 42%. Lower doses have not been found to be very effective in lowering homocysteine levels.

Vitamin B12 supplementation has also been found to decrease serum homocysteine levels by around 15%.

Pyridoxine hydrochloride supplementation, in the absence of vit B6 deficiency, was not found to significantly lower the serum homocysteine levels.

When all these 3 vitamins were given combinedly, orally or as a once monthly intramuscular injection, it was found to lower the homocysteine levels by 15-72%.

Since the combination of vit B6 and B12 with folic acid has a better effect in patients with low vit B6 or B12 levels, a combined therapy with all 3 vitamins is preferred for the treatment of hyperhomocysteinemia.

Also, when folate is given alone, it masks the vit. B12 deficiency. Various complications of vit B12 deficiency like subacute combined degeneration of spinal cord can be hence prevented with vit B12 supplementation.

The American Heart and Stroke Association advised to treat patients having stroke and hyperhomocysteinemia with 0.4 mg of folic acid, 2.4 µg of vitamin B12 and 1.7 mg of vitamin B6 daily.

N-Acetyl-Cysteine

Research studies have found that N-acetyl-cysteine (NAC) has a homocysteine lowering effect. Usage of this drug can lead to a highly significant reduction in atherosclerotic vascular events. This is attributable to the improvement of endothelial function by the homocysteine lowering ability of NAC. NAC promotes the formation of cysteine from homocysteine and also produces NAC disulphide molecules during the process, and these 2 molecules are easily excreted via the kidneys, and thus homocysteine levels in blood can be lowered.

Omega-3 PUFAs

Many researches have found that omega-3 fatty acids lower homocysteine levels. Therefore fish oils which are rich in omega-3 fatty acids can be given for treating hyperhomocysteinemia.

Taurine

It has been found that the amino acid taurine decreases methionine absorption from the diet, which in turn leads to less production of homocysteine in the body. Therefore, supplementation with taurine can decrease atherosclerotic vascular disease by lowering homocysteine levels in the blood.

Trimethylglycine (TMG) and Choline

TMG (Betaine) which was discovered from sugar beets, acts as a methyl donor in the homocysteine metabolism pathway, in the reaction where homocysteine is converted back into methionine. So more homocysteine is salvaged back into methionine, thereby lowering homocysteine levels.

Choline gets metabolised into TMG in our body.

Hence supplementation of TMG and choline can be useful in lowering serum homocysteine levels. These have been found to be useful for preventing atherosclerosis.

SAMe

SAMe (S-adenosyl-L-methionine), is a molecule which is directly involved in the synthesis and metabolism of homocysteine. It is biosynthesized from methionine and ATP. It also helps in conversion of homocysteine back into methionine as it acts as a methyl donor itself.

Nutritional supplementation of SAMe is useful for hyperhomocysteinemia, as it also promotes the conversion of homocysteine to glutathione and cysteine.

SAMe supplements also increase the activity of 5-MTHF, which converts homocysteine back into methionine.

Riboflavin

Vitamin B2 (riboflavin) has also been known to be a determinant of plasma homocysteine levels in individuals with a 5-MTHFR C677T gene variant. Hyperhomocysteinemia is highly responsive to riboflavin (since riboflavin is required as a co-factor by MTHFR), especially in individuals with the MTHFR C677T genotype.

CEREBROVASCULAR DISEASE

Cerebrovascular diseases include the following disorders – ischemic stroke, hemorrhagic stroke, cerebrovascular anomalies like intracranial aneurysms, AV malformations, etc.

These diseases are a main cause for mortality as well as morbidity worldwide.

Since the old age population is increasing (due to better medical care), the incidence of these diseases are also increasing, and they are more common in the older ages.

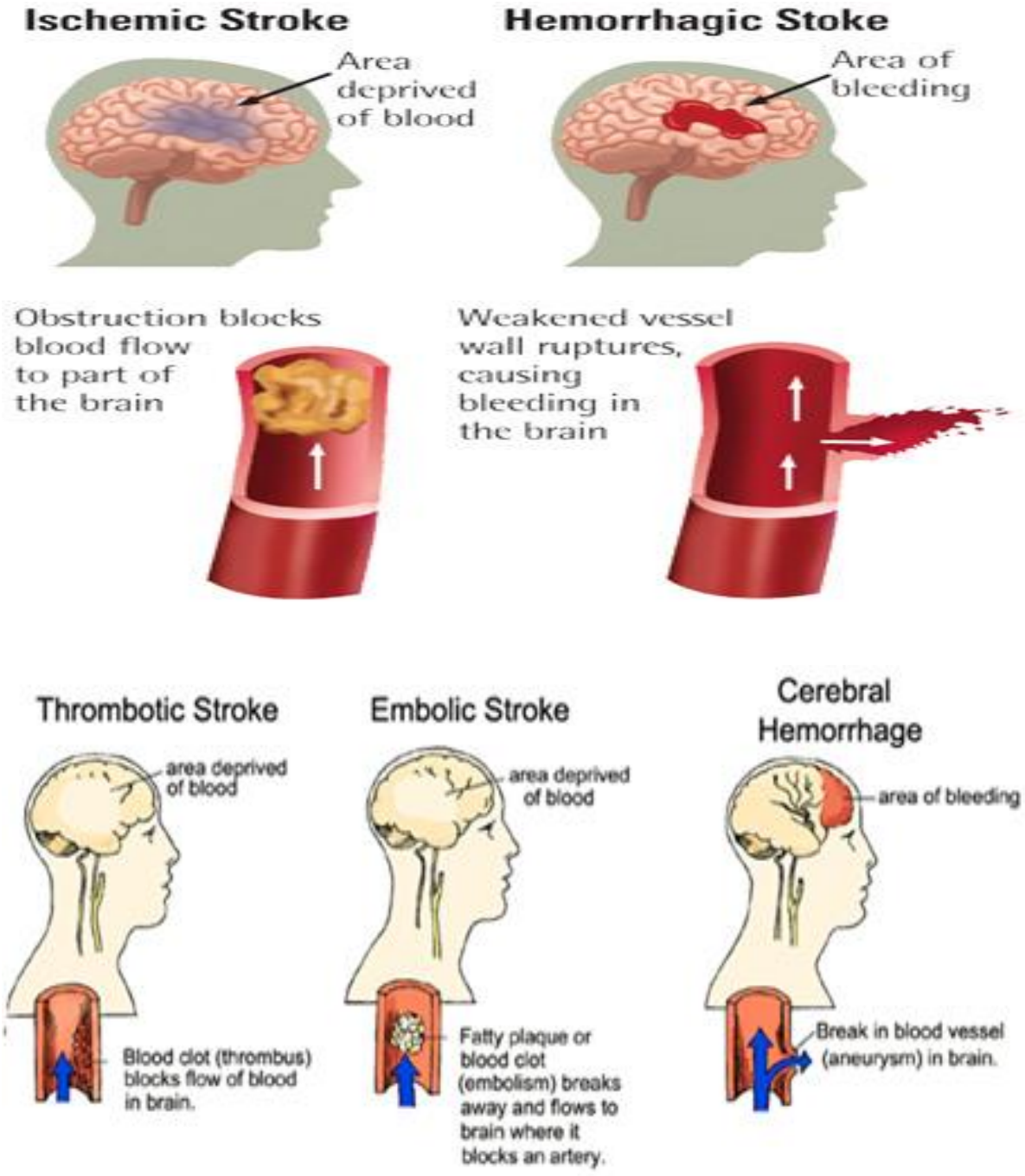
These diseases usually present in the form of a focal neurological deficit.

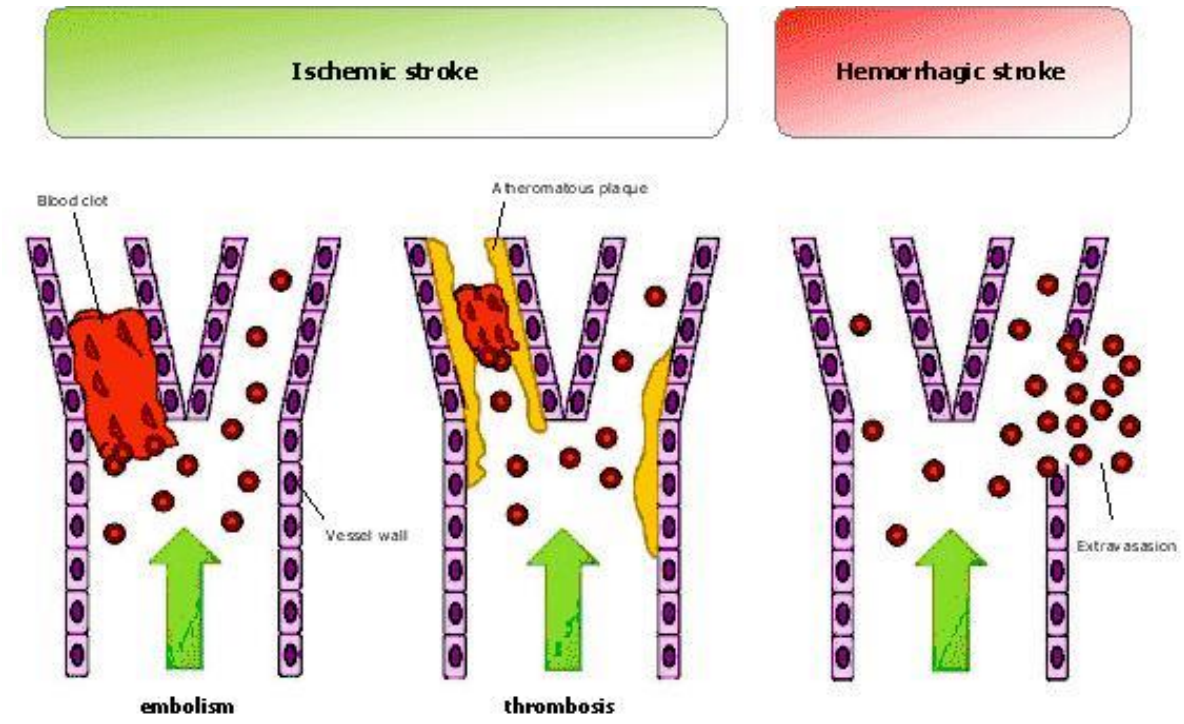
Stroke – a sudden onset of a neurological deficit , which is due to the interruption of blood supply to the brain, and which lasts for more than 24 hours. This results in damage to the brain tissue – *cerebral ischemia*. Neurological symptoms can be seen within seconds of blood supply disruption because neurons do not have glycogen and so energy failure occurs rapidly.

Cerebral infarction , that is, death of the neurons and the brain tissue occurs if the disruption of blood supply to the brain lasts for many minutes.

Ischemic stroke – caused by obstruction of blood flow in a vessel, caused by a thrombus or an embolus.

Hemorrhagic stroke – caused by bleeding from the blood vessels into or around the brain parenchyma. The symptoms and signs are caused by the blood itself or the mass effect of the bleed onto the surrounding brain structures or from increased intracranial tension.





Transient Ischemic Attack (TIA) - it has been dubbed as a 'mini-stroke', and it is defined as a transient episode of neurological deficit due to disruption of cerebral blood flow, but the neurological signs and symptoms resolve within 24 hours of onset. The diagnosis of TIA can be made even without imaging evidence of brain injury.

If the symptoms or signs persist for more than 24 hours, then we call it a stroke.

Hypoxic ischemic encephalopathy – this occurs when there is global cerebral ischemia, which in turn deprives the brain of adequate oxygen supply leading to cerebral hypoxia. The consequent neurological sequelae that follows is termed Hypoxic ischemic encephalopathy.

BRAIN - ANATOMY

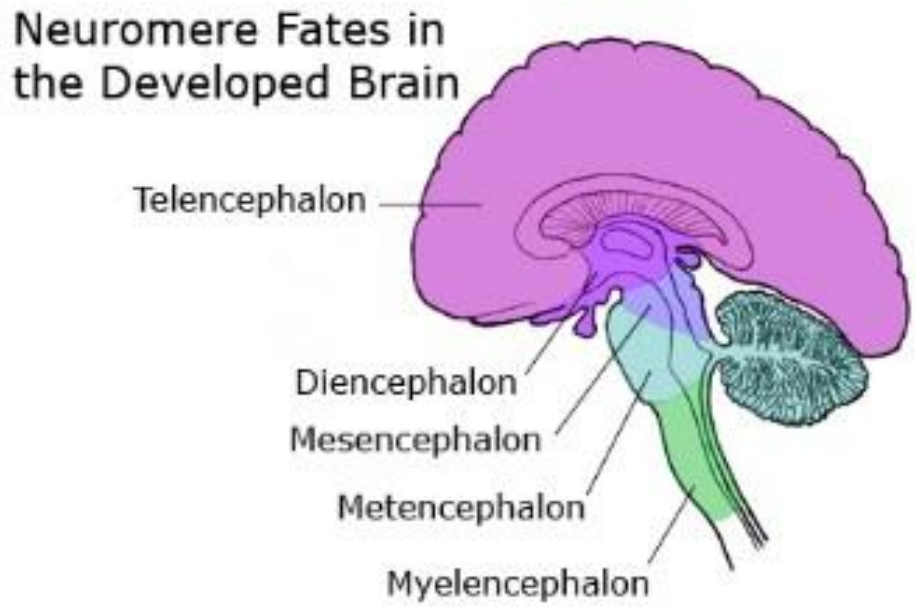
The adult human brain, on average, weighs about 1.5 kg and has a volume of around 1130 cm^3 in women and 1260 cm^3 in men.

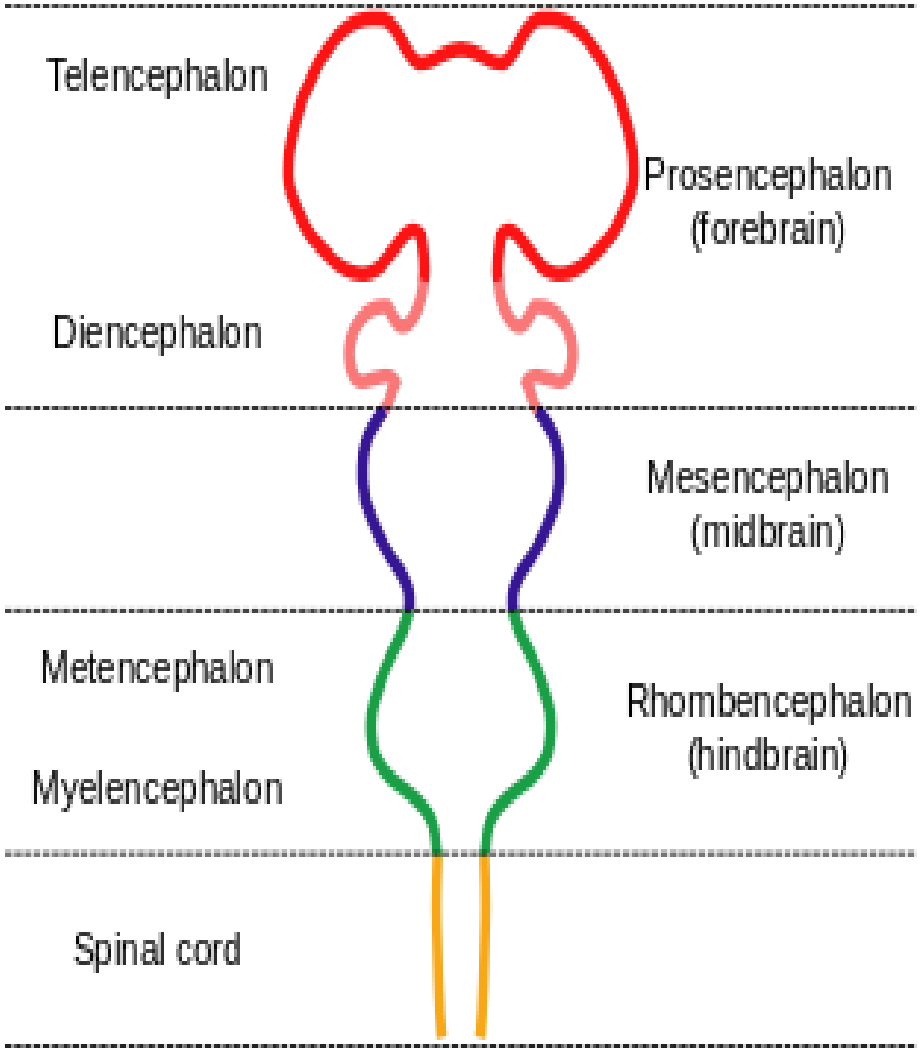
The brain lies within the cranial cavity and it is continuous with with the spinal cord through foramen magnum.

3 meninges surround the brain – the pia mater, arachnoid mater and the dura mater., which are continuous with the corresponding meninges of the spinal cord. The brain is surrounded by the cerebrospinal fluid in the subarachnoid space.

Anatomical division of brain can be done in several ways. The most common way of division is into 3 parts – Prosencephalon (forebrain), Mesencephalon (midbrain) and Rhombencephalon (hindbrain) – and this is based on the embryonic development.

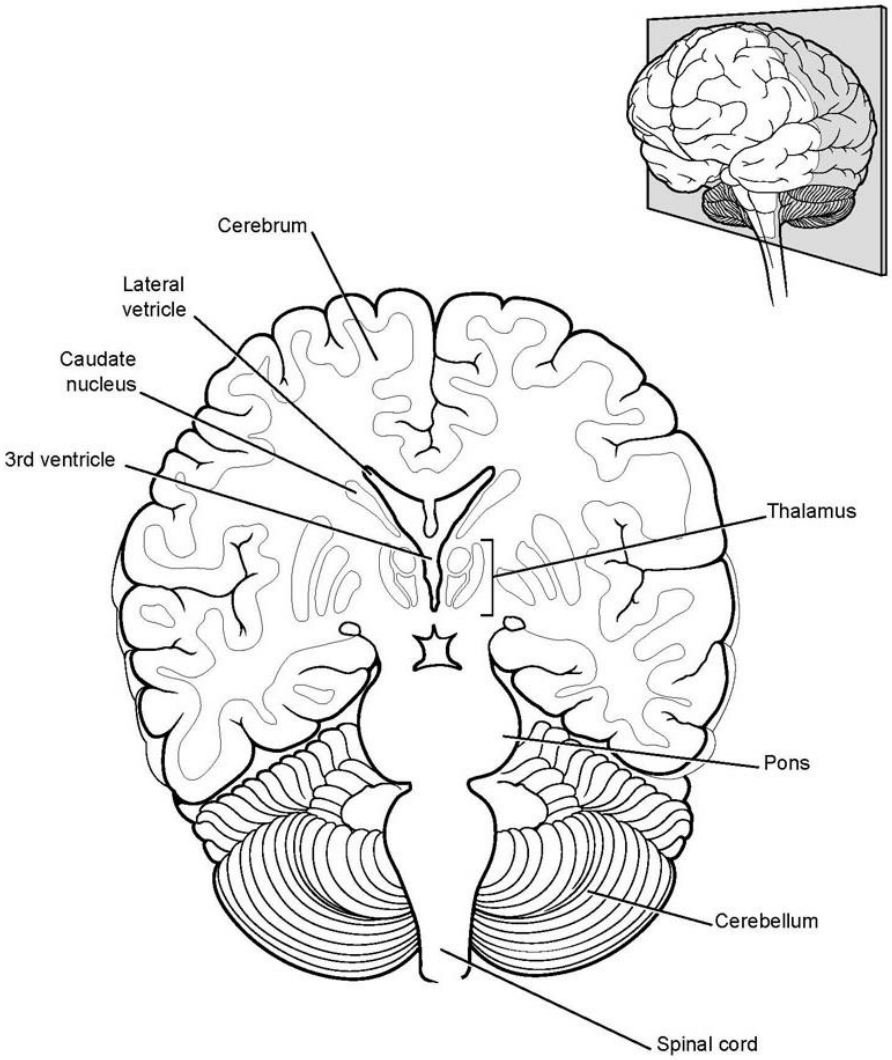
- The **forebrain** (**or *Prosencephalon)*** is made up of the cerebrum, thalamus and the hypothalamus. The cerebrum makes up the *Telencephalon* and the thalamus and hypothalamus and the rest constitute the *Diencephalon*.
- The **midbrain** (**or *Mesencephalon)*** is composed of the tectum (or corpora quadrigemina), the tegmentum, the cerebral aqueduct and the cerebral peduncles, which are part of the brainstem.
- The **hindbrain (or *Rhombencephalon*)** consists of the pons, the medulla oblongata and the cerebellum. The medulla forms the *Myelencephalon* and the pons & cerebellum form the *Metencephalon*.

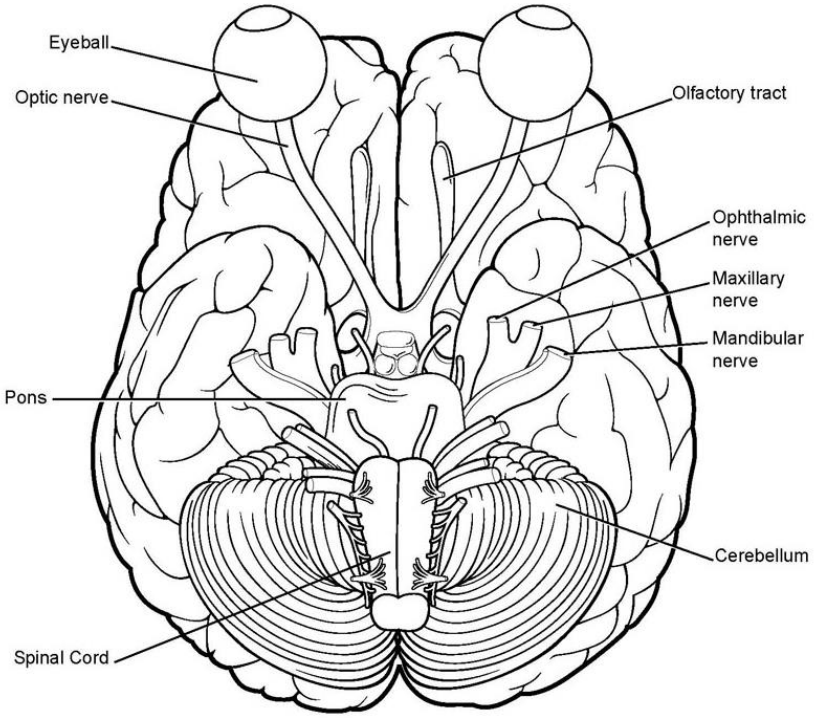

Neuromere Fates in
the Developed Brain
Telencephalon
Diencephalon
Mesencephalon
Metencephalon
Myelencephalon

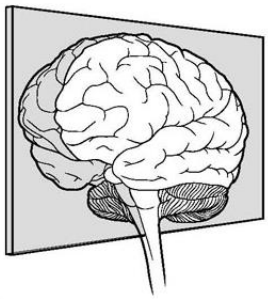

Telencephalon
Prosencephalon
(forebrain)
Diencephalon
Mesencephalon
(midbrain)
Metencephalon
Rhombencephalon
(hindbrain)
Myelencephalon
Spinal cord

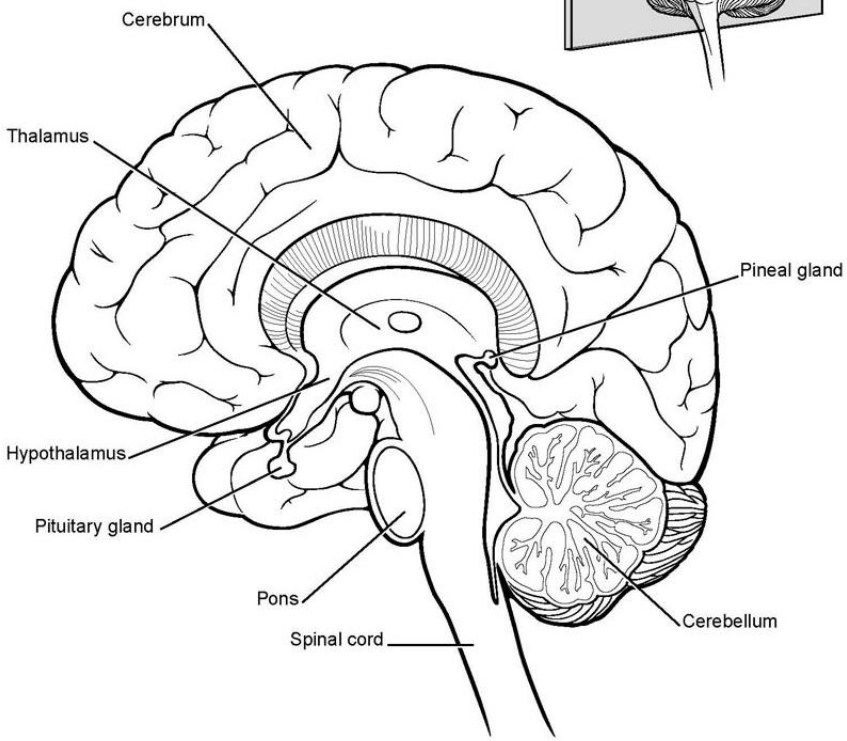
The brain tissue consists of an inner core of white matter and a surrounding outer covering of gray matter.

- *Gray matter* is mostly made of unmyelinated neurons, and most of them are interneurons. These gray matter regions are the main areas of nerve connections and processing.
- *White matter* is mostly made of myelinated neurons which connect the regions of gray matter to each other and also to the rest of the body. These myelinated neurons can transmit nerve signals much faster than unmyelinated axons.So the white matter acts as the information highway of the brain, by speeding the connections between distant parts of the brain and also the body.
- Certain important masses of gray matter are found deep inside within the white matter, eg. The cerebellar nuclei within the cerebellum, the gray thalamic, caudate and lentiform nuclei within the cerebrum.


Cerebrum
Lateral vetricle
Caudate nucleus
3rd ventricle
Thalamus
Pons
Cerebellum
Spinal cord


Eyeball
Optic nerve
Olfactory tract
Ophthalmic nerve
Maxillary nerve
Mandibular nerve
Pons
Cerebellum
Spinal Cord




Cerebrum
Thalamus
Pineal gland
Hypothalamus
Pituitary gland
Pons
Spinal cord
Cerebellum

Histology

Brain cells can be divided into two groups: the neurons and the neuroglia.

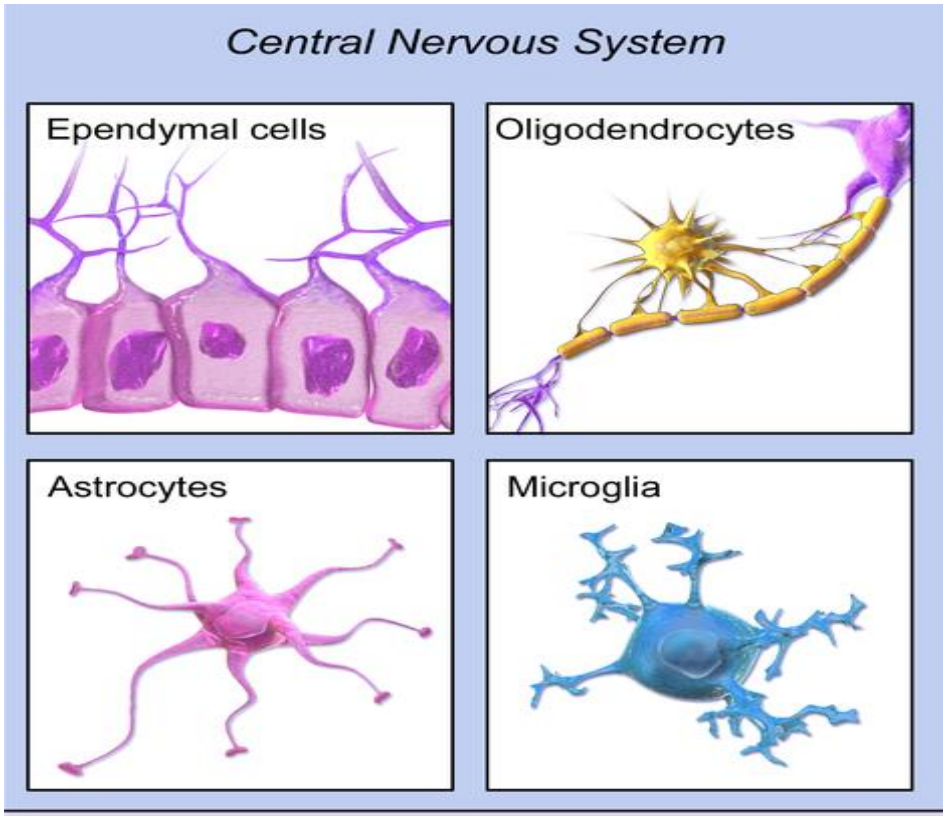
Neurons, or nerve cells, are those cells that perform all the communication and processing within the brain. Majority of the neurons in the brain's gray matter are interneurons, and these neurons are responsible for integrating and processing information which are delivered to the brain by the sensory neurons. Sensory neurons which enter the brain from the peripheral nervous system deliver information regarding the condition of the body and its surroundings. Interneurons then send signals to the motor neurons, which then carry signals to muscles and glands.

Neuroglia, or glial cells, are the helper cells of the brain. These cells support and protect the neurons. There are four types of glial cells in the brain namely - astrocytes, oligodendrocytes, microglia, and ependymal cells.

- *Astrocytes* act by protecting neurons, by filtering nutrients out of the blood and also preventing pathogens and chemicals from leaving the capillaries of the brain. Astrocytes are the predominant building blocks for the blood brain barrier.
- *Oligodendrocytes* act by wrapping the axons of neurons in the brain to produce an insulation known as myelin. These myelinated axons transmit nerve signals

much faster than unmyelinated ones, therefore oligodendrocytes accelerate the communication speed of the brain.

- *Microglia* act similar to white blood cells by attacking and destroying pathogens that invade the brain. They are specialized macrophages which are capable of phagocytosis thereby protecting neurons of the central nervous system.
- *Ependymal cells* are those which line the capillaries of the choroid plexuses and produce cerebrospinal fluid.



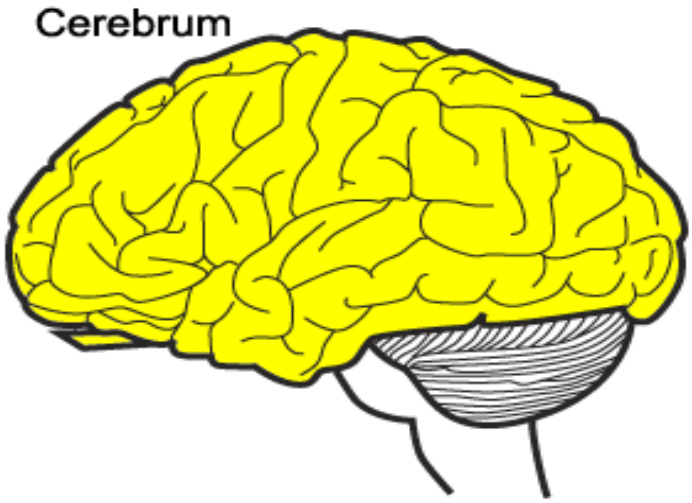
CEREBRUM

The cerebrum is the largest part of the brain. It develops from the telencephalon. It lies in front or on top of the brainstem. In humans, it is the largest and best-developed part of the major divisions of the brain. The cerebrum is the phylogenetically newest structure in the brain. The surface layer of the cerebral hemispheres, that is the cortex, is thrown into folds or gyri, and are separated by fissures or sulci. This results in an increased surface area of the cerebral cortex. The largi sulci are used to subdivide the surface of the cerebral hemispheres into lobes.

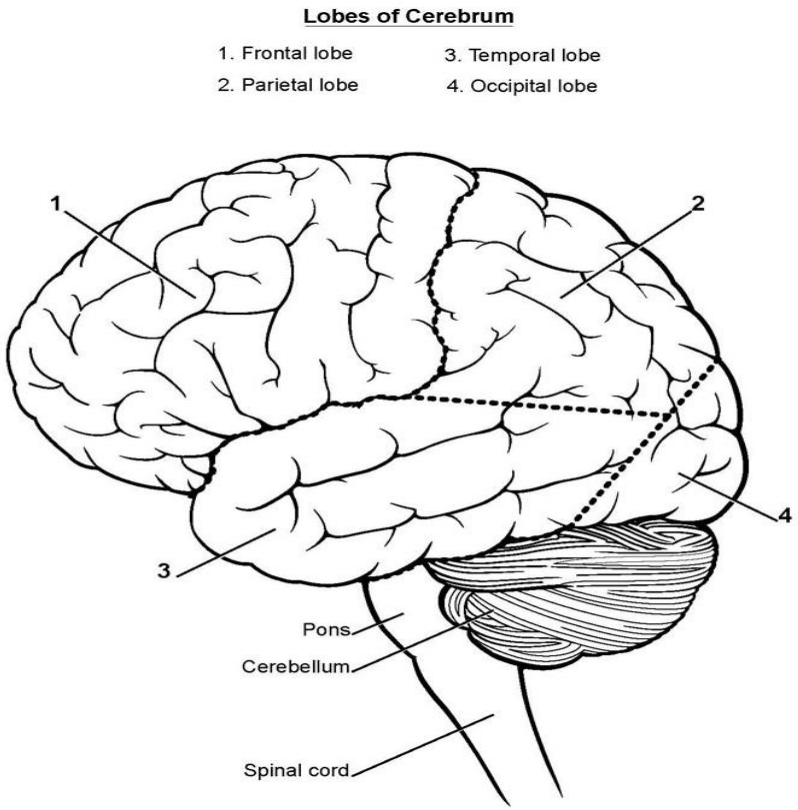
The cerebrum is made of the following regions:

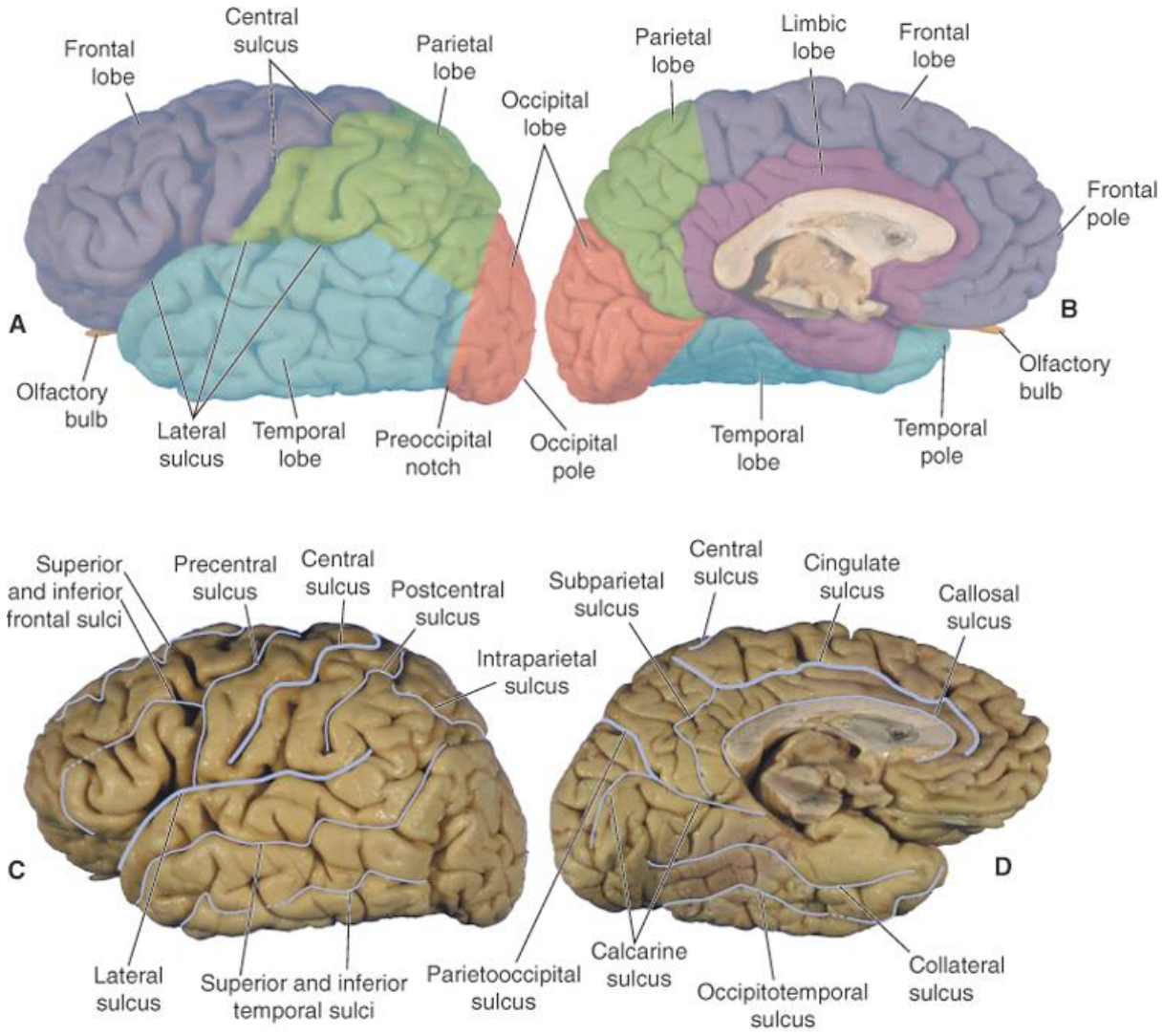
- Cerebral cortex or the cortices of the cerebral hemispheres
- Basal ganglia
- Limbic System

The limbic and motor systems project fibres from the cerebrum to the brainstem and spinal cord. Cognitive systems project fibres from the cerebrum to the thalamus and to some specific regions of the midbrain. These neural networks of the cerebrum facilitate complex behaviors such as thought, judgement, social interactions, working memory, learning, speech and language.


Cerebrum

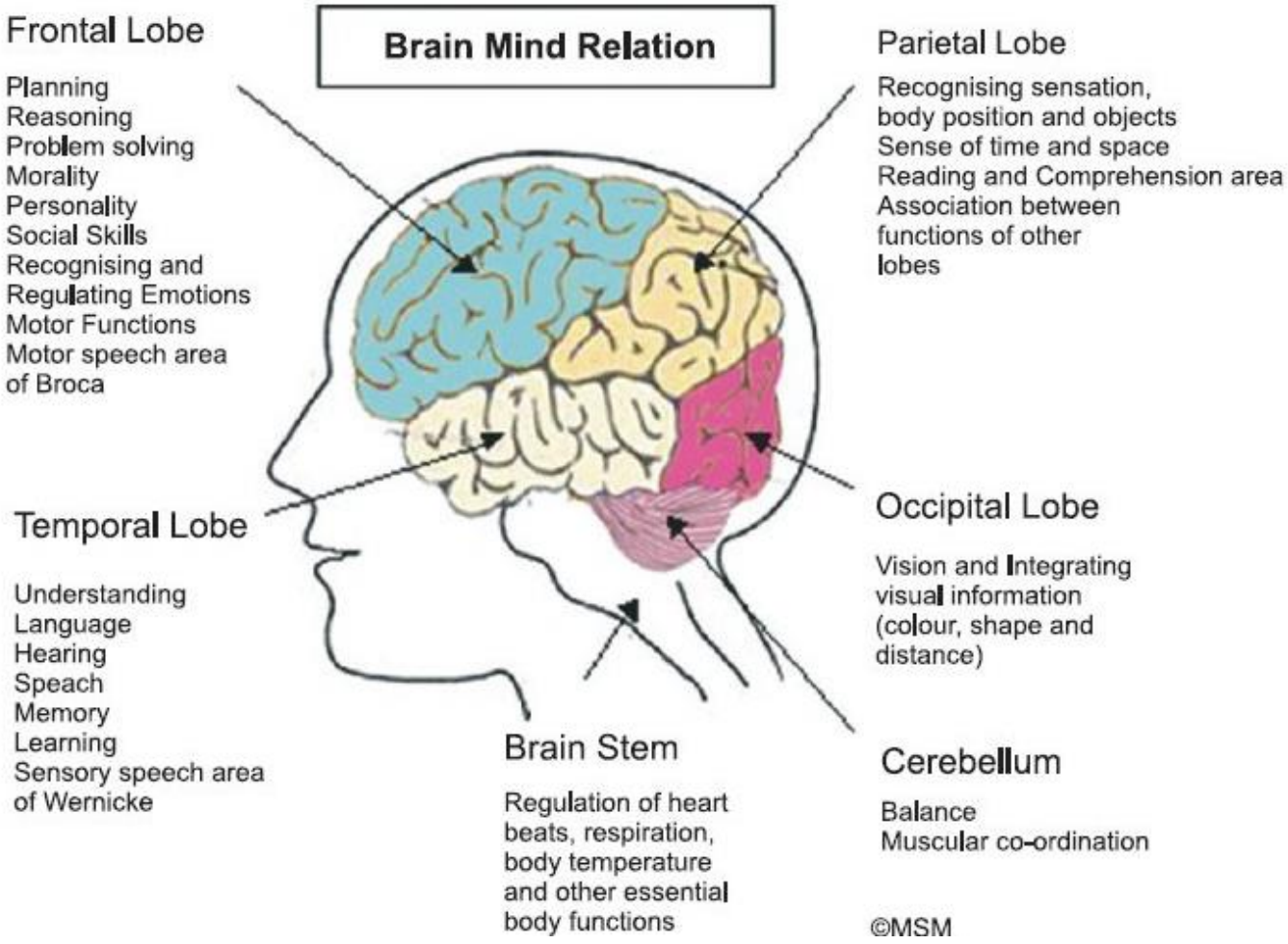
LOBES


Lobes of Cerebrum
1. Frontal lobe
2. Parietal lobe
3. Temporal lobe
4. Occipital lobe
1
2
3
4
Pons
Cerebellum
Spinal cord



The cerebrum is divided into 4 lobes –

1. Frontal lobe
2. Parietal lobe
3. Temporal lobe
4. Occipital lobe


Brain Mind Relation
Frontal Lobe
Planning
Reasoning
Problem solving
Morality
Personality
Social Skills
Recognising and
Regulating Emotions
Motor Functions
Motor speech area
of Broca
Parietal Lobe
Recognising sensation,
body position and objects
Sense of time and space
Reading and Comprehension area
Association between
functions of other
lobes
Temporal Lobe
Understanding
Language
Hearing
Speach
Memory
Learning
Sensory speech area
of Wernicke
Occipital Lobe
Vision and Integrating
visual information
(colour, shape and
distance)
Brain Stem
Regulation of heart
beats, respiration,
body temperature
and other essential
body functions
Cerebellum
Balance
Muscular co-ordination
©MSM

BRAIN CIRCULATION – ANATOMY

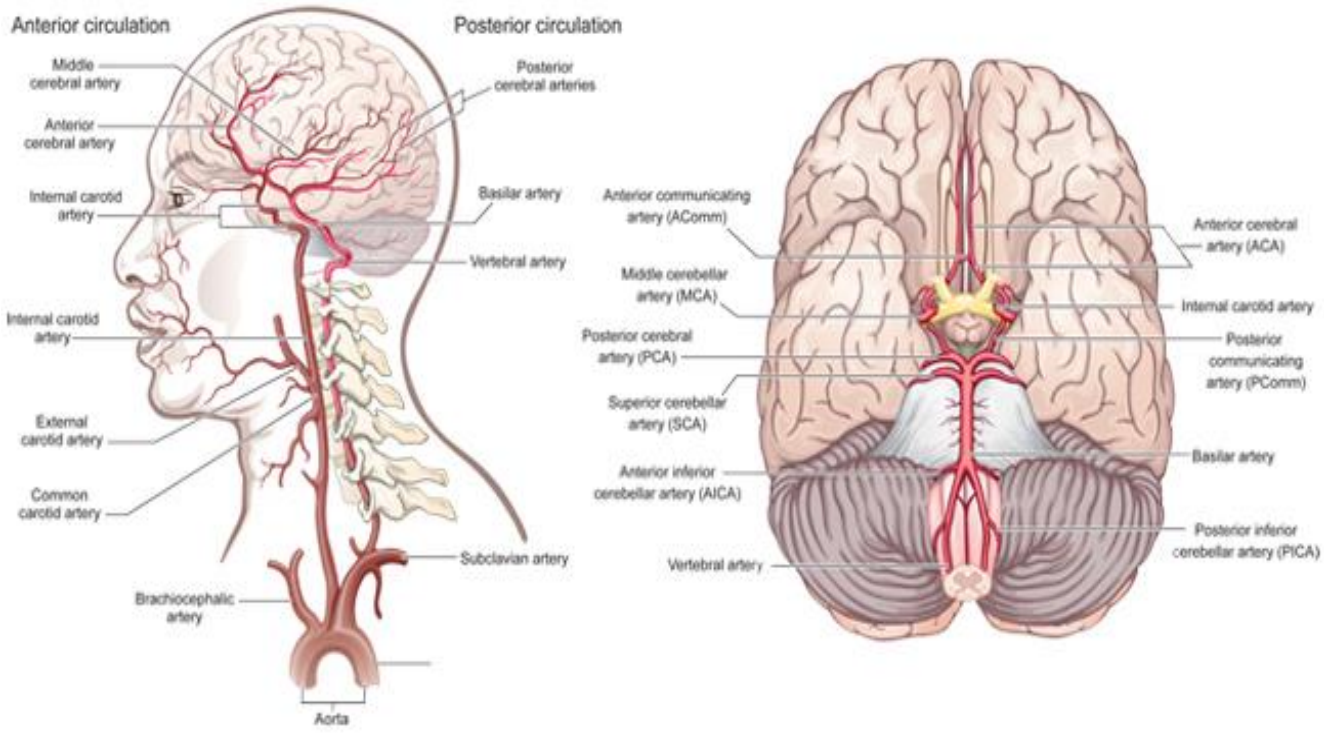
The cerebral circulation has an arterial circulation and a venous drainage.

The arterial circulation of the brain can be divided into :

1. Anterior circulation
2. Posterior circulation

A stroke can occur involving either the anterior circulation, posterior circulation or both.

The major artery in the anterior circulation is the internal carotid artery whereas the vertebral artery is the one for the posterior circulation.

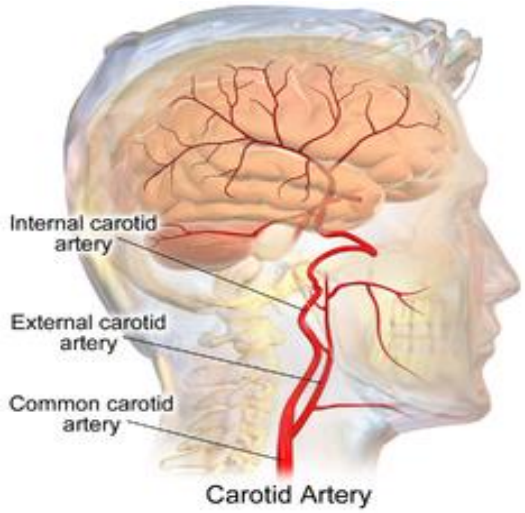


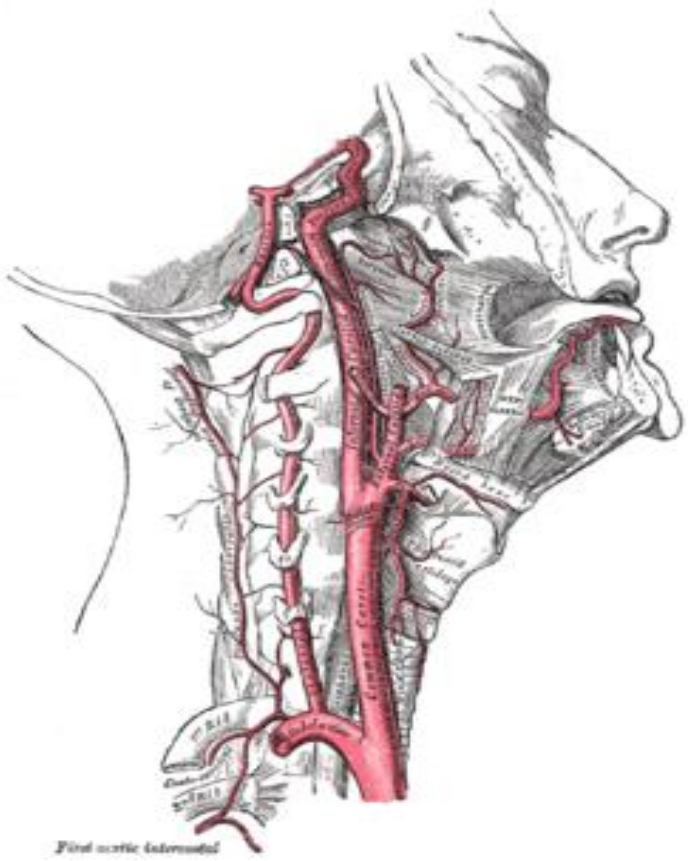
ANTERIOR CIRCULATION

Anterior circulation is by the 2 internal carotid arteries which lie in the subarachnoid space, and they anastomose with the vertebral artery branches on the inferior surface of the brain to form what is called the *circle of willis.*

Internal carotid artery –

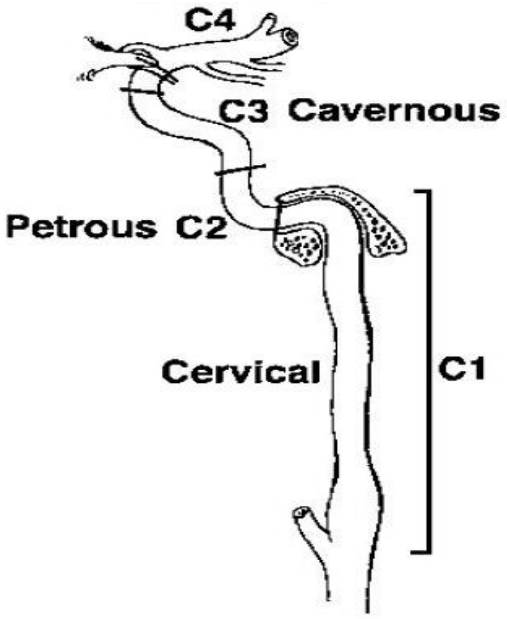
It begins where the common carotid artery bifurcates into the external and internal carotid arteries , at c3-c5 level, where it has a localised dilatation called the carotid sinus. It ascends through the neck and enters the skull through the base of the skull and passes through the carotid canal of the temporal bone. Then it runs forward in the cavernous sinus before piercing the dura mater and emerging on the medial side of the anterior clinoid process. Here it pierces the arachnoid mater and enters the subarachnoid space where it turns posteriorly towards the medial end of the lateral cerebral sulcus and there it divides into the anterior and middle cerebral arteries.



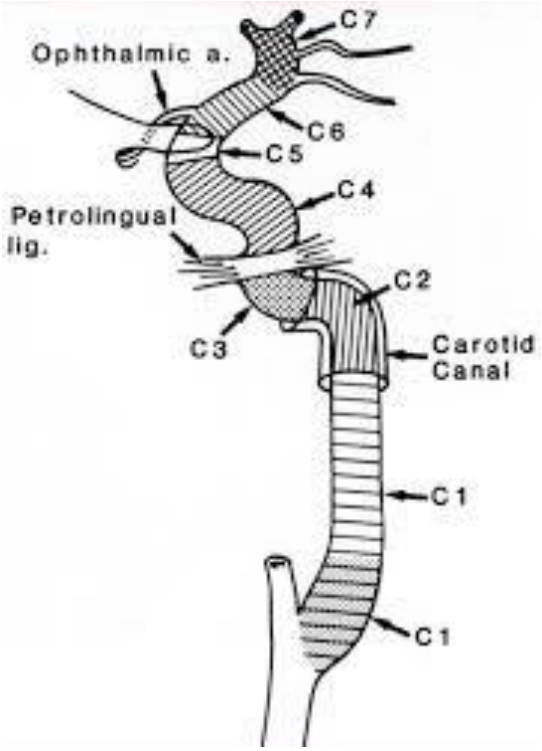


The internal carotid artery is divided into 4 portions based on its course :

1. Cervical
2. Petrous
3. Cavernous
4. Cerebral

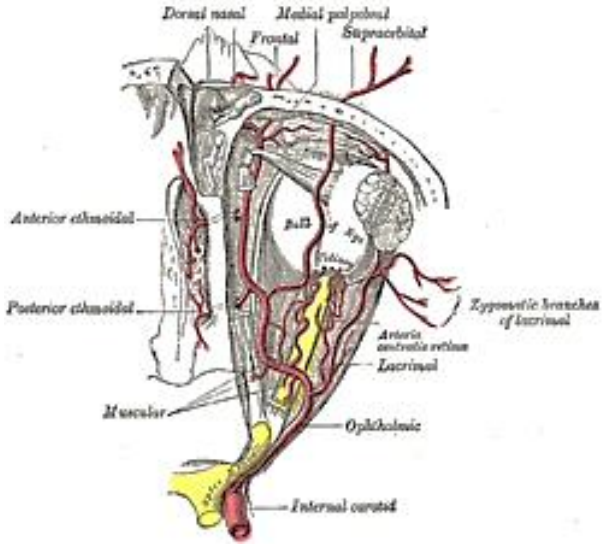


Bouthellier also divided the internal carotid into 7 segments namely - C1 cervical, C2 petrous, C3 lacerum, C4 cavernous, C5 clinoid, C6 ophthalmic, and C7 communicating.



Branches of the cerebral segment :

1. Ophthalmic artery – it is the first branch of the internal carotid, which is given off as the internal carotid leaves from the cavernous sinus. It is given off along the medial side of the anterior clinoid process and it enters the orbit through the optic canal with the optic nerve running inferolaterally.



Area of supply – eye, orbital structures, frontal area of scalp, dorsum of nose , frontal and ethmoid sinuses.

Branches - Central retinal artery, Lacrimal artery, Posterior ciliary arteries, Muscular branches, Supraorbital artery, Ethmoidal arteries, Medial palpebral arteries, supratrochlear (frontal) artery and the dorsal nasal artery.

2. Posterior communicating artery

   It is a small blood vessel which takes off from the internal carotid artery very near its terminal bifurcation and it then runs posteriorly to join the posterior cerebral artery, thus it connects the anterior and posterior circulation and forms a part of the circle of willis. This artery functions like a collateral between the anterior and posterior circulations of the brain.

3. Choroidal artery

   It originates from the posterior wall of the internal carotid near its terminal bifurcation and passes posteriorly near the optic tract, then it circumvents the cerebral peduncles to reach the lateral geniculate body. It enters the lateral ventricle and finally ends in the choroid plexus. It mainly supplies the lateral geniculate body, the crus cerebri , optic tract and internal capsule.

4. Anterior cerebral artery

   It is one of the terminal branches of the internal carotid, along with the middle cerebral artery, and it is the smaller of the two. It runs forward, medially and superiorly to the optic nerve and enters the longitudinal fissure of the cerebrum, then curves backward and passes anterior to the genu of corpus callosum, and anastomoses with the posterior cerebral

artery. The anterior cerebral arteries on either side are interconnected by the anterior communicating artery.

The cortical branches supply medial surface of cerebral cortex and a thin strip of the lateral surface as well. It supplies most of the superior medial parietal lobes and parts of the frontal lobes.

The central branches pierce the anterior perforated substance and supply the corpus callosum, the lentiform and caudate nuclei as well as the internal capsule.

5. Middle cerebral artery

It is the other terminal branch and the largest branch of the internal carotid artery. It runs laterally in the cerebral sulcus and divides into many cortical and central branches and mainly supply the lateral cortex and internal capsule.

Cortical branches supply almost whole of lateral cerebral hemisphere except for the superior inch of the frontal and parietal lobe (anterior cerebral artery supply), the occipital pole and inferolateral surface (posterior cerebral artery supply).

Central branches supply the basal ganglia and internal capsule.

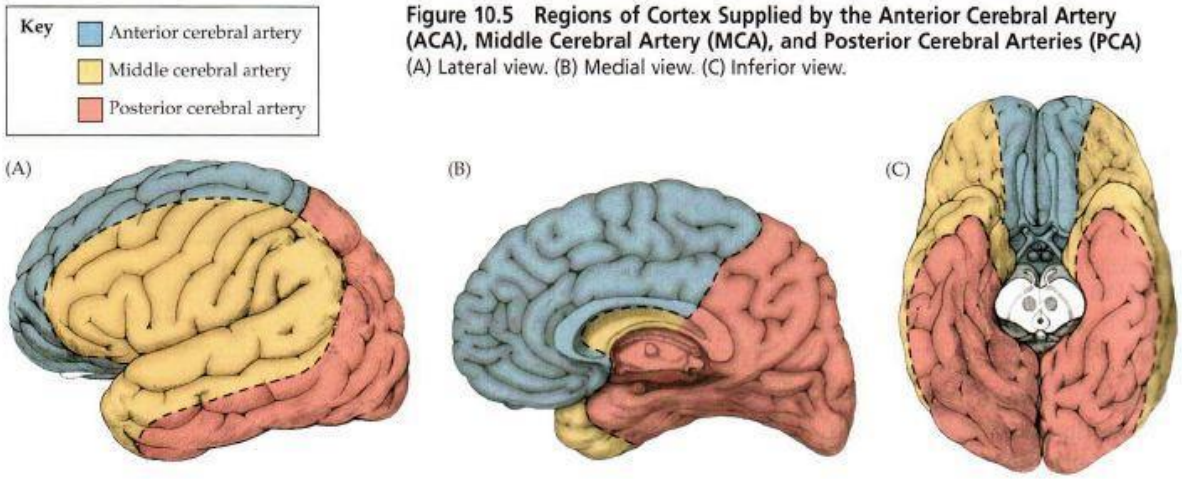
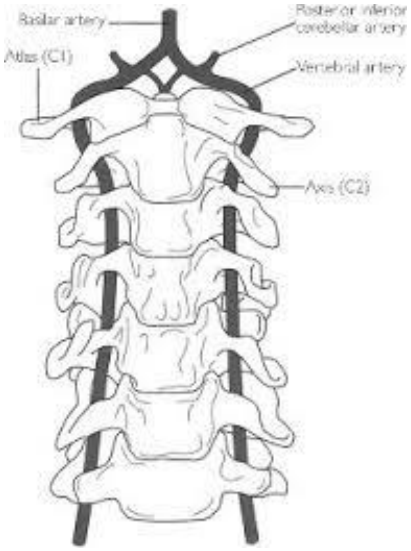
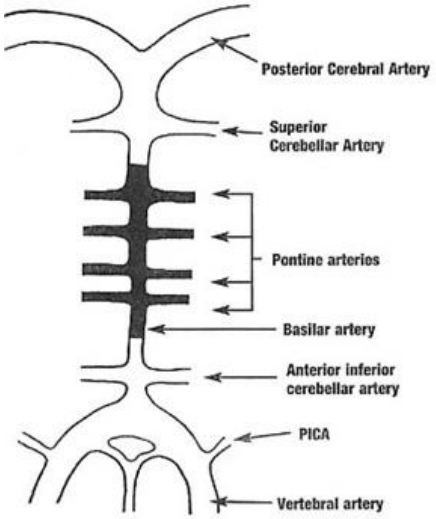


Figure 10.5 Regions of Cortex Supplied by the Anterior Cerebral Artery (ACA), Middle Cerebral Artery (MCA), and Posterior Cerebral Arteries (PCA)
(A) Lateral view. (B) Medial view. (C) Inferior view.

POSTERIOR CIRCULATION





Vertebral artery :

The vertebral arteries arise from the 1st part of the subclavian artery, passes deep to the transverse processes of the 6th cervical vertebra, then ascends up the neck by passing through the foramina in the transverse processes of the above cervical vertebrae. They cross the posterior arch of C1 and pass in the suboccipital triangle before it enters the skull through the foramen magnum. They then pierces the dura and arachnoid to enter the subarachnoid space. They ascend and when they reach the lower border of pons, they join to form the basilar artery.

Branches :

1) Meningeal branches
2) Posterior spinal artery
3) Anterior spinal artery
4) Posterior inferior cerebellar artery
5) Medullary branches

Basilar artery :

It is formed by the confluence of the right and left vertebral arteries, and then it ascends in a groove on the anterior surface of the pons. When it reaches the upper border of pons, it divides into the posterior cerebral arteries.

The vertebral and basilar arteries together constitute the vertebrobasilar system.

Branches of basilar artery :

1) Pontine arteries
2) Labyrinthine artery
3) Anterior inferior cerebellar artery
4) Superior cerebellar artery
5) Posterior cerebral artery

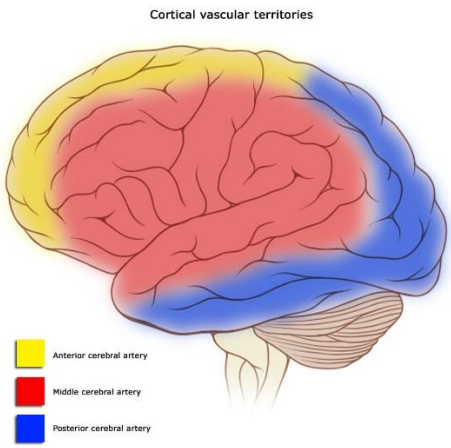
Posterior Cerebral Artery :

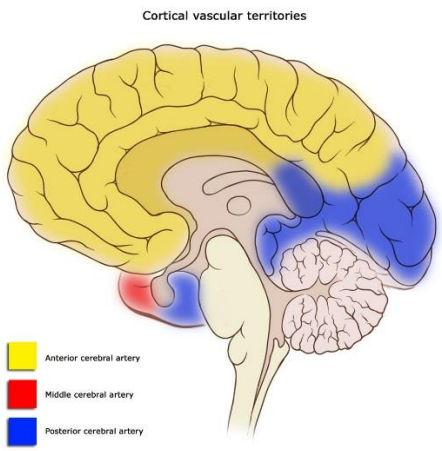
It is the terminal branch of the basilar artery. It curves around the midbrain where the posterior communicating artery joins it.

Cortical branches of the posterior cerebral artery supply the occipital lobes and posteromedial temporal lobes.

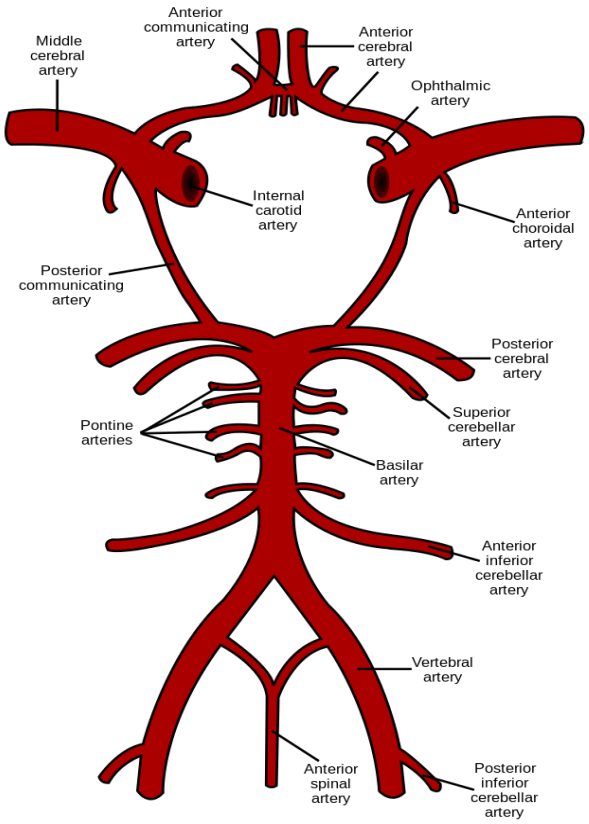
Central branches supply the thalamus, lentiform nucleus, midbrain, pineal gland and medial geniculate bodies.

A choroidal branch supplies the choroid plexus of the 3rd ventricle.





CIRCLE OF WILLIS



The circle of willis , also called circulus arteriosus cerebri, is an anastomotic system between the 2 internal carotid and the 2 vertebral arteries, which lies in the interpeduncular fossa encircling the pituitary stalk.

Importance – this creates collaterals in the brain circulation. If any part / artery of this circle is narrowed or thrombosed, blood flow from the other arteries prevent ischemia by preserving the cerebral perfusion.

Vessels forming the circle of willis – anterior communicating , internal carotid, anterior cerebral, posterior communicating, posterior cerebral and basilar arteries.

ISCHEMIC STROKE

Ischemic stroke is the result of obstruction of blood flow in a blood vessel supplying to an area of the brain.

2 types :

1) Thrombotic stroke

2) Embolic stroke

Thrombotic stroke – due to a thrombus formed inside the blood vessel.

It is again divided into 2 – large vessel thrombosis and small vessel thrombosis.

Embolic stroke – due to a blood clot that was formed elsewhere in the body circulation, which breaks loose and travels in the circulation to reach the brain vessels and causes ischemia of the brain tissue.

Ischemic strokes are the most common type of strokes and it accounts for around 87% of all strokes.

Incidence of ischemic stroke increases with age and risk factors like diabetes, smoking, hypertension, heart disease, dyslipidemia, etc.

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

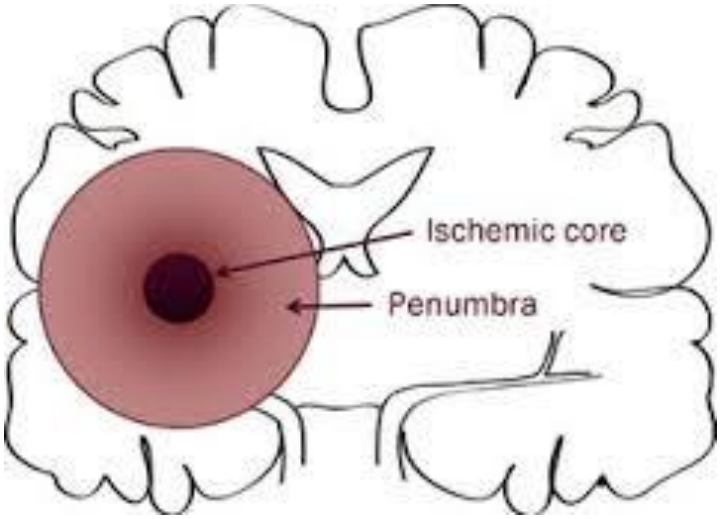
When there is an acute obstruction of an intracranial blood vessel, there is a reduction in blood flow to the particular area it supplies. The physiological and anatomical protective mechanisms come into action like autoregulation of cerebral blood flow , collateral circulation , etc. These depend on individual vascular anatomy, site of occlusion , systemic blood pressure and various other factors. When these are overcome, cerebral ischemia ensues. The time take for the death of brain tissue depends on the volume of decrease of the cerebral blood flow.

If cerebral blood flow is absent or zero, death of brain tissue occurs in 4 – 10 minutes.

Cerebral blood flow < 16-18 ml/100g tissue/min causes brain tissue death within an hour.

Cerebral blood flow < 20ml/100g/min causes ischemia but not infarction unless prolonged for several hours or days.

Ischemic penumbra – refers to the area surrounding the core region of infarction which is ischemic but reversibly dysfunctional. The penumbra remains viable due to the collateral supply. If no change in blood flow or restoration of blood flow does not occur, the ischemic penumbra will also infarct.

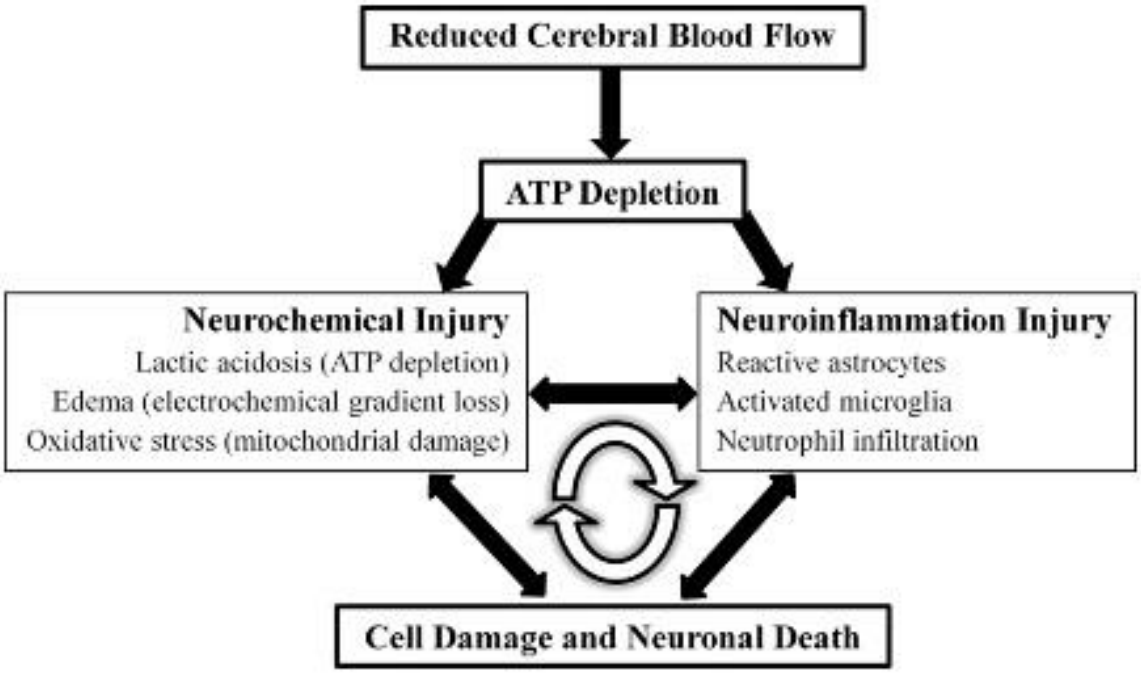


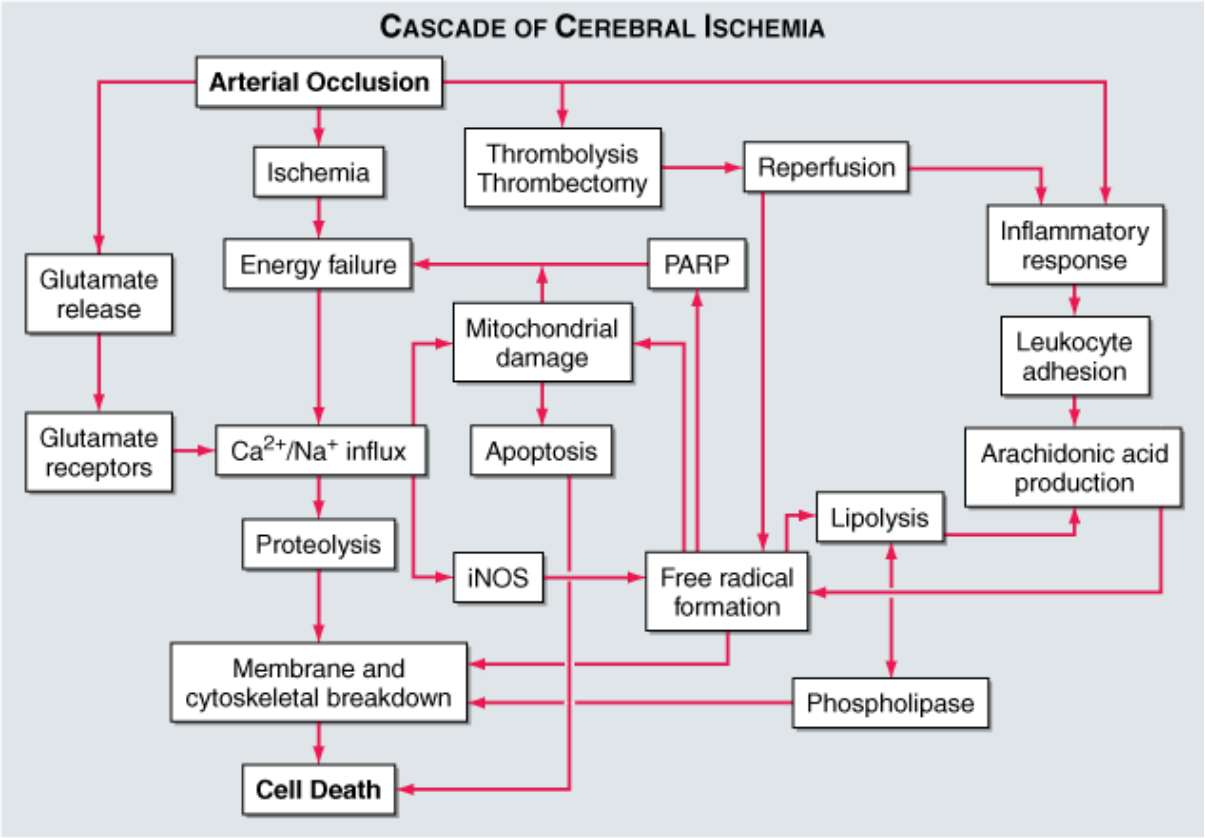
MECHANISMS OF ISCHEMIC INJURY :

1) Cerebral edema leading to increased intracranial tension
2) Microvascular thrombosis – caused by inflammatory mediators like TNF – alpha, interleukins,..etc.
3) Apoptosis – programmed cell death
4) Infarction with cell necrosis

Necrotic cell death is due to –

1) Loss of ATP stores
2) Loss of ionic homeostasis – intracellular calcium accumulation
3) Cell membrane damage due to free radicals
4) Glutamate and other excitatory neurotoxins
5) Lactate accumulation leading to intracellular acidosis





PARP – poly-A ribose polymerase; iNOS - inducible nitric oxide synthase

RISK FACTORS

MODIFIABLE	NON- MODIFIABLE
Physical inertia	Old age
Smoking	Male gender
Hypertension	Blacks
Dyslipidemia	Positive family history
Diabetes Mellitus	Past history of stroke
Atrial fibrillation	Genetic problems
Diet	

CAUSES OF ISCHEMIC STROKE

A) Thrombosis – lacunar stroke (small vessel), large vessel thrombosis, dehydration

B) Embolic occlusion –

- Artery to artery – carotid bifurcation, aortic arch, arterial dissection
- Cardioembolic – atrial fibrillation, mural thrombus, myocardial infarction, dilated cardiomyopathy, valvular lesions, bacterial

endocarditis, paradoxical embolus (ASD, patent foramen ovale), atrial septal aneurysm, spontaneous echo contrast.

C) Hypercoagulable disorders – protein C deficiency, protein S deficiency, antithrombin III deficiency, antiphospholipid syndrome, factor V leiden mutation, ***hyperhomocysteinemia,*** sickle cell anemia, polycythemia vera, SLE, nephrotic syndrome, TTP, IBD, OCPs, etc.

D) Others – venous sinus thrombosis, fibromuscular dysplasia, vasculitis, drugs (cocaine, amphetamine), moyamoya disease, eclampsia.

SIGNS AND SYMPTOMS :

When a patient comes with an abrupt onset of focal neurological deficit or an altered level of consciousness , stroke should be suspected.

The clinical signs and symptoms vary according to the artery involved and the site of lesion in the brain.

The most common symptoms and signs of stroke are hemiparesis, hemisensory loss, altered sensorium, seizures, aphasia, dysarthria, visual disturbances, ataxia, vertigo, deviation of angle of mouth, etc.

These signs and symptoms can occur in isolation but usually they are seen in a combination.

Headache, projectile vomiting , sudden loss of consciousness are more common in hemorrhagic strokes.

Suspect stroke if there is -

Sudden Onset of:

- Numbness or weakness of the face, arms, or legs
- Confusion, trouble speaking or understanding speech
- Trouble seeing in one or both eyes
- Trouble walking, dizziness, loss of balance or coordination
- Severe headache with no known cause

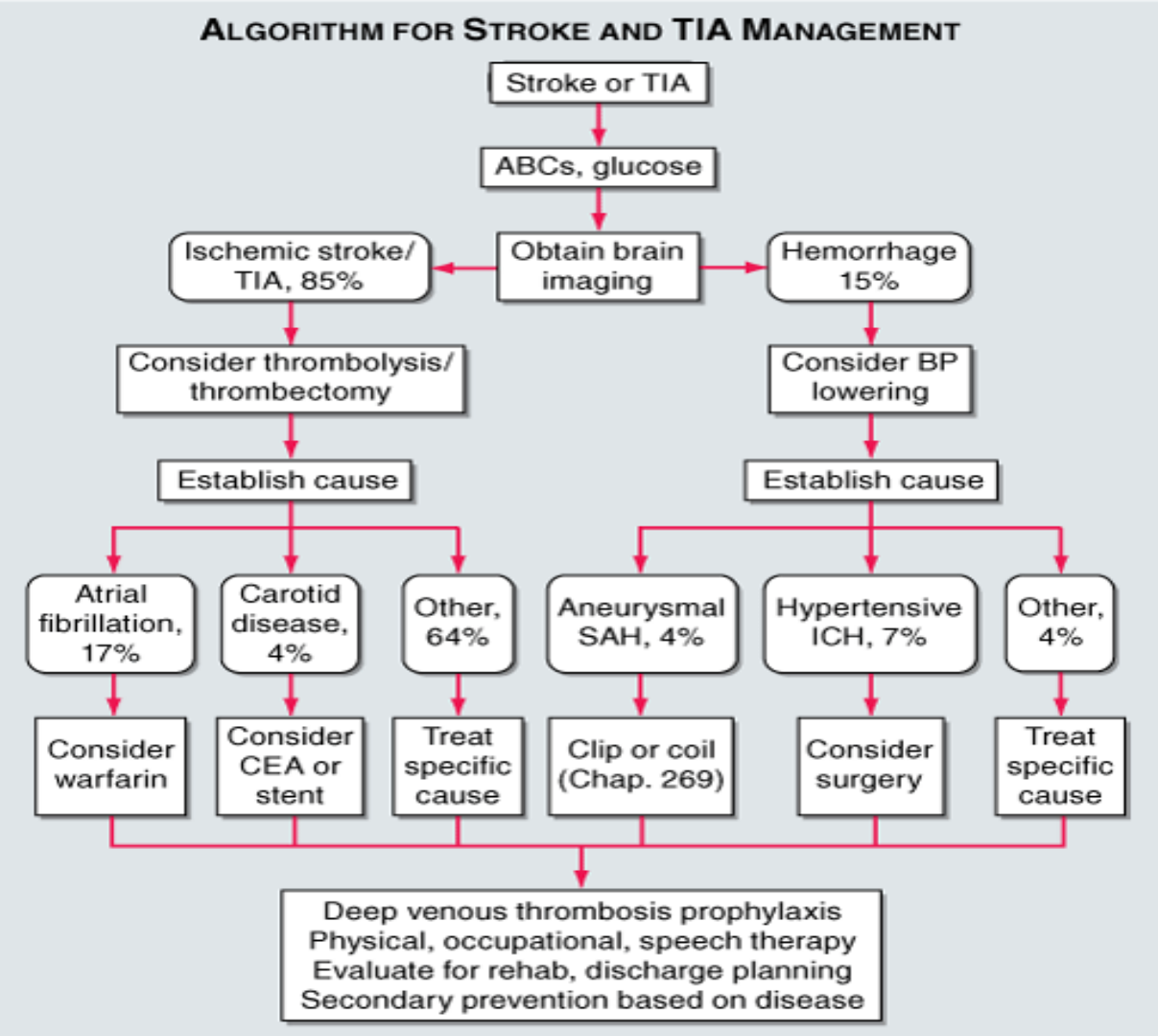
Dominant Hemisphere	Non-dominant Hemisphere
• Sequential • Analytical • Verbal • Logical • Mathematics: perception of counting/ measurement • Present and past • Language: grammar/ words, pattern perception, literal	• Simultaneous • Holistic • Imagistic • Intuitive • Perception of shapes • Present and future • Intonation/ emphasis, prosody, pragmatic, contextual

Type of Circulation	Symptoms
Anterior	
Carotid artery	Contralateral motor and sensory loss
	Amaurosis fugax (transient blindness) or transmonocular blindness caused by emboli to retinal artery
Anterior cerebral artery (ACA)	Confusion
	Personality change
	Incontinence
	Contralateral motor or sensory loss leg greater than arm
Middle cerebral artery (MCA)	Contralateral motor or sensory loss (arm greater than leg)
	Contralateral motor loss in lower face
	Contralateral visual field loss
	Language loss (dominant hemisphere)
	Spatial-perceptual loss (nondominant hemisphere)
Posterior	
Posterior cerebral artery (PCA)	Contralateral motor or sensory loss
	Ipsilateral visual field loss
	Cortical or bilateral blindness
	Dysarthria
	Dysphagia
	Diplopia
	Quadriparesis
Vertebrobasilar	Altered brainstem and cerebellar functions
	Cranial nerve deficits for cranial nerves III–XII
	Ataxia
	Bilateral blindness or hemianopia
	Confusion
	Diplopia
	Bilateral limb weakness
	Bilateral paresthesias
	Slurred speech
	Vertigo

COMPLICATIONS OF STROKE

EARLY (< 7 DAYS)	**LATE (> 7 DAYS)**
Cerebral edema, herniation	Decubitus ulcer
Hemorrhagic transformation of infarct	contractures
Recurrent infarction , increase in size of infarct	Depression, psychological disturbances
Aspiration pneumonitis	Decubitus ulcers
Seizures	Aspiration pneumonitis
Gastrointestinal ulcers, bleeds	DVT, pulmonary embolism
DVT, pulmonary embolism	Urinary tract infections (catheterisation)

APPROACH TO THE PATIENT



IMAGING STUDIES :

1) CT scans – they are the standard imging study for identifying or excluding haemorrhage as the cause of stroke. Ischemic strokes cannot be reliably picked up by a CT scan in the initial 24-48 hours. They are also not useful for small ischemic strokes in the posterior fossa. Because it is cheaper, faster and more readily available than other imaging modalities, non contrast CT is the imaging of choice for acute stroke.

2) MRI – even though MRI is less sensitive than CT for detecting blood, it readily and reliably identifies the location and extent of infarcts in all areas of the brain. Early brain infarction can be detected by the diffusion weighted sequences and the FLAIR sequences.

3) Cerebral angiography – gold standard for detecting and quantifying atherosclerotic stenosis of cerebral arteries.

4) Xenon CT and PET – used to quantify cerebral blood flow.

5) Transcranial Doppler – to assess MCA, ACA, PCA and vertebrobasilar flow.

TREATMENT OF ACUTE ISCHEMIC STROKE

The treatment aim of acute ischemic stroke is to save the area of ischemic penumbra. Tissue plasminogen activator (tPA) is the only FDA approved treatment for ischemic strokes. It has to be administered within 3 hours (4.5 hours in select cases) of onset of symptoms for a beneficial effect. This time interval is important, that's why early identification of sympyoms /signs and early hospitalisation is important. Streptokinase is not used because of a higher incidence of intracranial haemorrhage and death.

Endovascular procedures - Mechanical thrombectomy – are also being practised in select centres for acute ischemic strokes. 4 devices have been approved for mechanical thrombectomy namely Merci Retriever, Penumbra system, Solitaire FR Revascularization Device and Trevo.

325 mg of oral aspirin has also been recommended within 24-48 hours of onset of ischemic stroke.

Primary prevention – use of antiplatelets, statins, dietary modifications and exercise in patients with no previous history of stroke and those who are at high risk for stroke.

Secondary prevention – use of antiplatelets, antihypertensives, statins and others to prevent recurrence in a patient who already had stroke.

Physical, occupational and speech therapists also have an important role.

HYPERHOMOCYSTEINEMIA AND ISCHEMIC STROKE

Hyperhomocysteinemia has been found to be an independent risk factor for ischemic stroke. Homocysteine levels more than 15 μmol/L is considered to be associated with an increased risk of ischemic stroke.

Hyperhomocysteinemia creates a proatherogenic and prothrombotic environment in the blood vessels.

The main mechanism for this is endothelial cell injury. This initiates the atherosclerotic cascade.

Other mechanisms include disruption of the normal clotting mechanisms by inhibition of factor C & antithrombin III and activation of factors 5 ,10 and 12. It increases thromboxane A2 synthesis leading to platelet aggregation. It causes smooth muscle proliferation, decreases nitric oxide release and increases production of free radicals.

All these factors occurring in the cerebral blood vessels lead to formation of a thrombus in these vessels, leading to ischemic stroke.

Patients with hyperhomocysteinemia in ischemic stroke should undergo routine ischemic stroke treatment (tPA/ endoscopic revascularisation/ aspirin) but along with that they should receive vitamin supplementation with adequate folic acid and vitamin B12 supplements.

CAROTID INTIMA MEDIA THICKNESS (CIMT)

The carotid intima media thickness is now routinely measured by non invasive methods like USG, CT, etc.

B-mode USG is the most commonly used technique for measuring CIMT. It can be used to evaluate the carotid lumen diameter and presence & extent of plagues as well.

Increased CIMT has been found to be an early marker of atherosclerosis. It has been shown in various studies that increased CIMT is a powerful predictor of coronary and cerebrovascular complications.

Advantages of CIMT by USG – relatively inexpensive, non invasive, no radiation hazards and is repeatable.

CIMT > 0.9 mm is associated with an increased cardiovascular and cerebrovascular risk.

Since homocysteine plays an important role in the pathogenesis of atherosclerosis, CIMT of patients with hyperhomocysteinemia can be used for predicting future cardiovascular and cerebrovascular problems. It has been found that homocysteine levels correlate with their CIMT measurements.

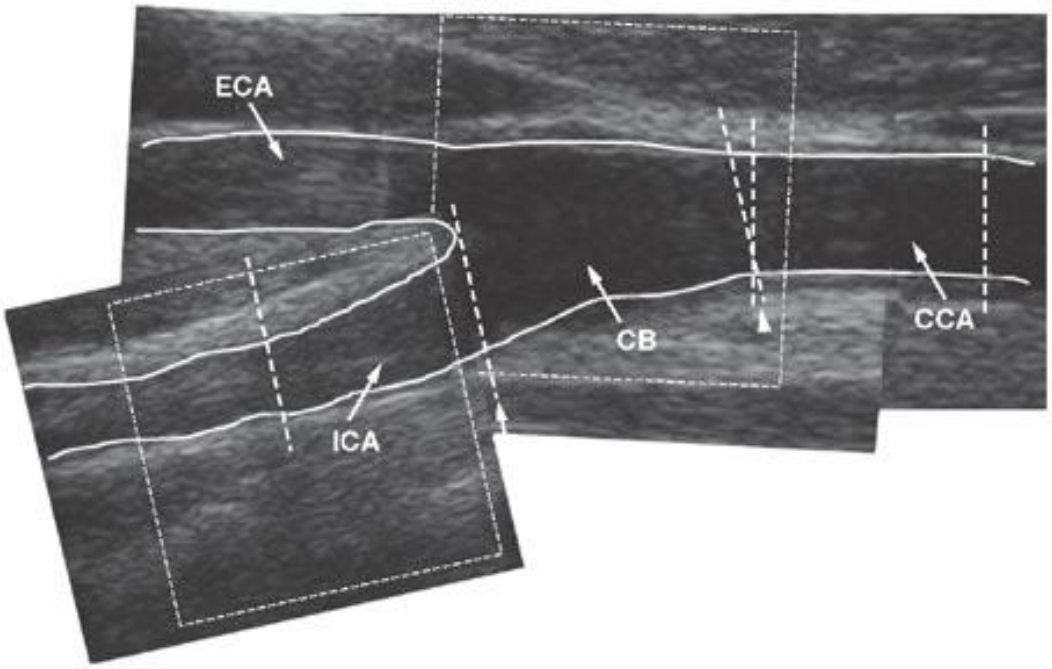
TECHNIQUE :

CIMT represents the combined thickness of the intima and media layers of the common carotid artery.

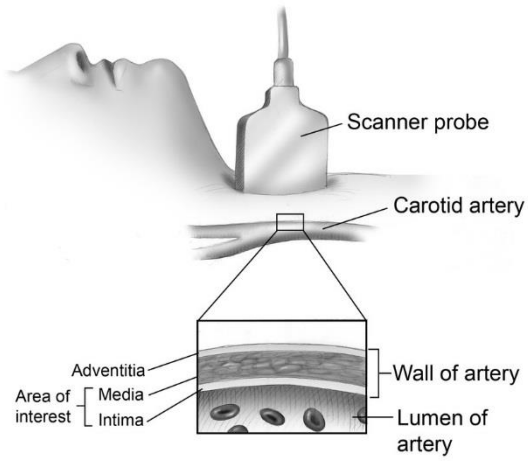
During routine ultrasound study, the carotid is divided into 3 segments, each segment measuring around 1 cm in length :

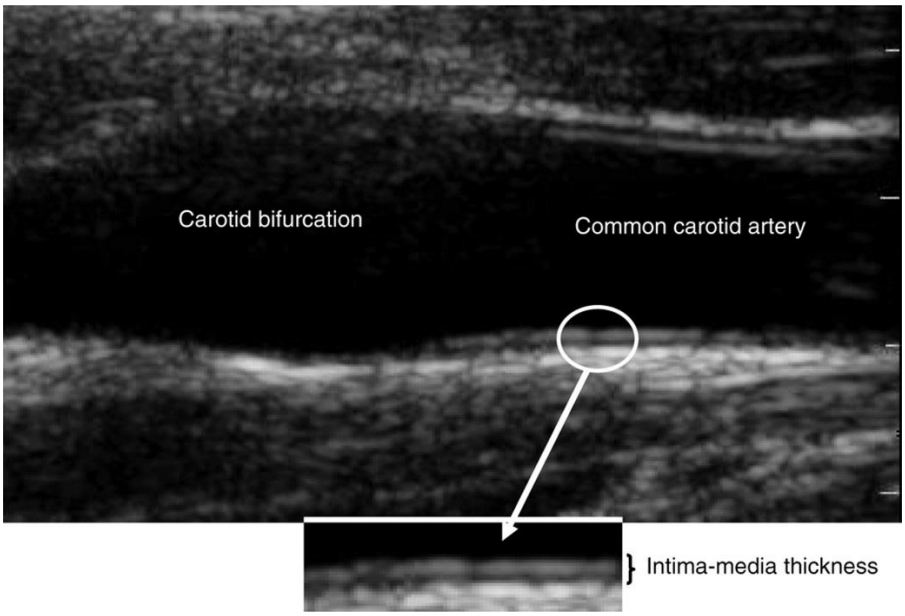
1) The common carotid artery just prior to its bifurcation
2) The carotid bulb at its bifurcation point
3) Proximal 1 cm of the Internal carotid.

The common carotid artery just prior to its bifurcation is the most commonly used area to measure CIMT.



The typical B-mode image shows 2 parallel echogenic lines separated by a hypoechoic space. These lines are the lumen-intima interface and the media-adventitia interface. Border detection programs are used to measure this space, they trace the leading edges of the lumen-intima to the leading edge of media-adventitia, and thus calculate the CIMT.





III. AIMS AND OBJECTIVES

1. To study the clinical profile of ischemic stroke at Government Stanley Hospital, Chennai.

2. To study prevalence of hyperhomocysteinemia in these patients and correlate with carotid intima media thickness in these patients.

IV. MATERIALS AND METHODS

Place of study:

Department of general medicine, medical OPD and medical wards, Stanley medical college and hospital, Chennai.

Duration:

November 2013 to September 2014.

Study design:

Prospective observational study

Patient selection:

Any patient with ischemic stroke in medical OPD and medical wards.

Sample size :

75 patients

Ethical committee approval

Ethical committee approval was obtained for the study

Methodology

Patients admitted with symptoms suggestive of ischemic stroke, which is proved later by CT brain, will undergo serum homocysteine measurements and carotid USG to measure carotid intima media thickness. The study will be aimed at observing the prevalence of hyperhomocysteinemia in ischemic stroke and also whether there is any correlation between the serum homocysteine levels and carotid intima media thickness.

Exclusion criteria:

Hemorrhagic stroke, patients on folic acid supplements, patients on anti-epileptics/ OCPs/ drugs causing hyperhomocysteinemia, chronic kidney disease, pre-existing coronary artery disease

Stastical analysis

Data will be analysed with SPSS software version 16.0 for windows.

All continuous data will be expressed as mean and sd and will be analysed using students t test.

Categorical data will be expressed as number (percentage) and analysed by chi square or fishers exact test.

Pearson's correlation coefficient and linear regression analysis will be undertaken to establish correlation and regression among variables.

P value of <0.05 was considered as statistically significant

CONSENT

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up for this study after getting a written / informed consent from these patients or their relatives in the local vernacular language.

STUDY SUBJECTS

All the patients who fulfilled the inclusion criteria were included in this study. The included patients were subjected to detailed history taking, complete physical examination and the relevant laboratory investigations as per a proforma, exclusively designed for the study.

V. RESULTS AND DISCUSSION

STATISTICAL ANALYSIS

Descriptive statistics was done for all data and suitable statistical tests of comparison were done. Continuous variables were analysed with the student's t test and categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using EpiInfo software (7.1.0.6 version; Center for disease control, USA) and Microsoft Excel 2010.

SAMPLE SIZE CALCULATION

Sample size was determined on the basis of a pilot study in which the difference in carotid intimal thickness in serum homocysteine groups was measured at 4%. We calculated a minimum sample size of 59 patients was required, assuming a type 1 error (two-tailed) of 0.05 and a margin of error of 10%. Therefore, the final sample selected was n= 75.

$$\mathbf{n} = \frac{\mathbf{t^2 \times p(1-p)}}{\mathbf{m^2}}$$

Description:

n = required sample size

t = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of malnutrition in the project area

m = margin of error at 10% (standard value of 0.05)

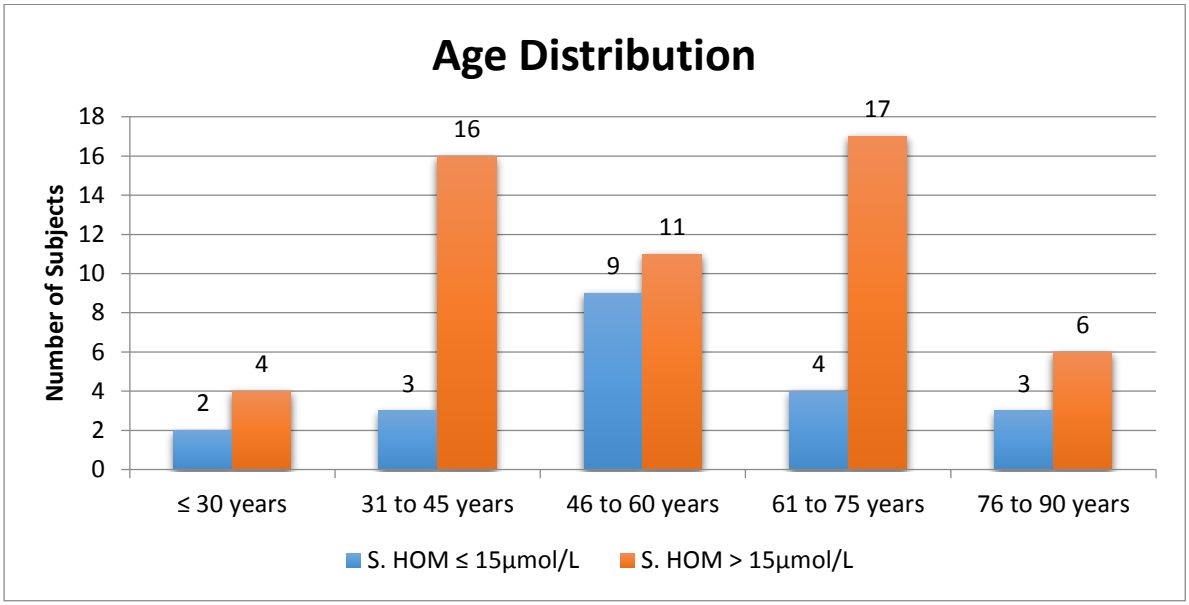
$$\mathbf{n} = \frac{\mathbf{(1.96)^2 \times 0.04(10865)}}{\mathbf{(0.05)^2}}$$

$$\mathbf{n} = \frac{\mathbf{3.8146 \times 0.0384}}{\mathbf{0.0025}}$$

= 59

= 75 samples in the study group

AGE

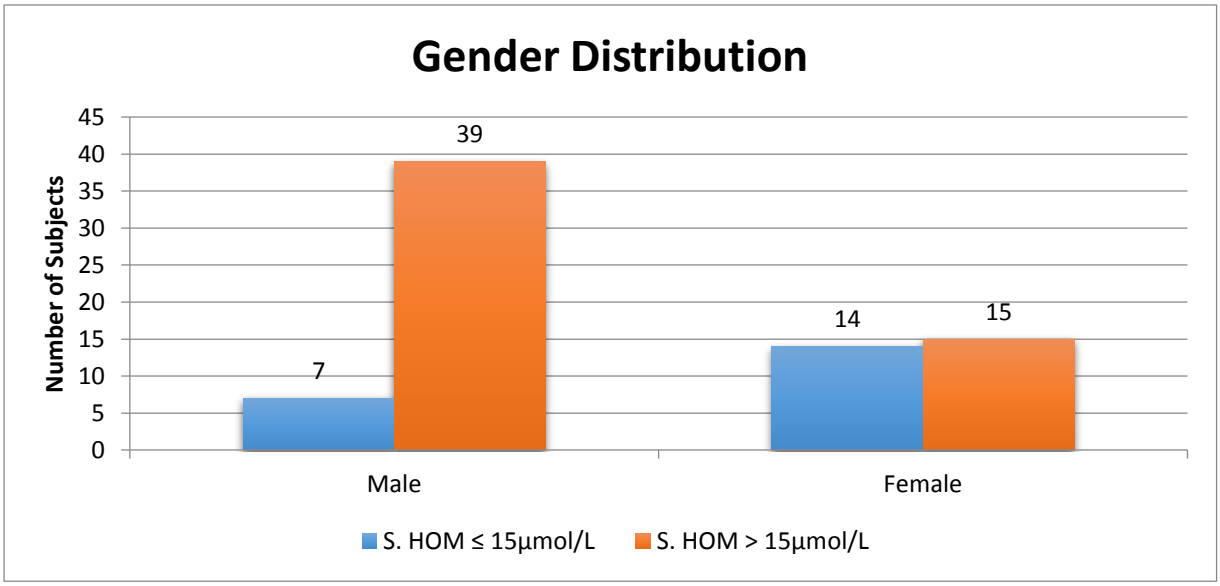


Age Distribution	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%
≤ 30 years	2	9.52	4	7.41
31 to 45 years	3	14.29	16	29.63
46 to 60 years	9	42.86	11	20.37
61 to 75 years	4	19.05	17	31.48
76 to 90 years	3	14.29	6	11.11
Total	21	100	54	100

Age Distribution	S. HOM ≤ 15µmol/L	S. HOM > 15µmol/L
N	21	54
Mean	55.66667	55.87037
SD	14.51666	16.75128
P value Unpaired t- test	0.9586	

By conventional criteria the association between the serum homocysteine groups and age is considered to be not statistically significant since p > 0.05.

GENDER



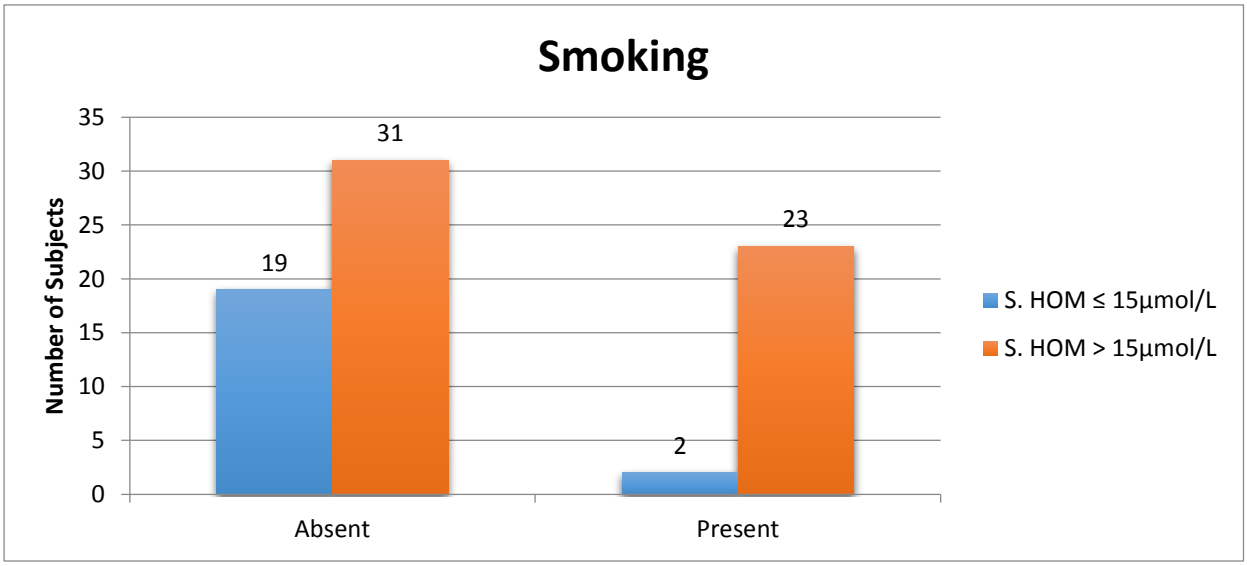
Gender Distribution	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%
Male	7	33.33	39	72.22
Female	14	66.67	15	27.78
Total	21	100	54	100
Chi-square Statistic		9.64		
Degrees of freedom		1		
P value Chi Squared Test		.200		

By conventional criteria the association between the serum homocysteine groups and Gender is considered to be not statistically significant since p > 0.05.

Since age and gender is not statistically significant, it means that there is no difference between the groups. In other words the groups contain subjects with the same basic demographic characteristics.

Risk Factors

Smoking



Smoking	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	
Absent	19	90.48	31	57.41
Present	2	9.52	23	42.59
Total	21	100	54	100
Chi-square Statistic		9.41		
Degrees of freedom		1		
P value Chi Squared Test		0.002		

By conventional criteria the association between the serum homocysteine groups and smoking is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of smoking is 2 in patients with serum homocysteine levels ≤ 15µmol/L and 23 in patients with serum homocysteine levels > 15µmol/L with a p-value of 0.002 according to Chi-Squared test.

Clinical Significance

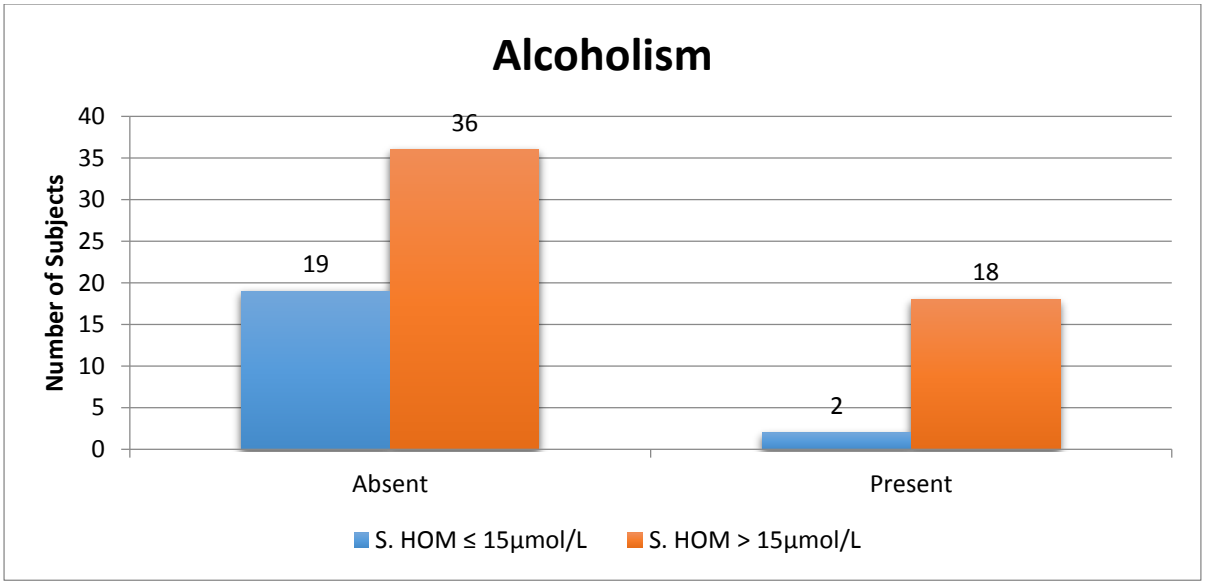
The incidence of smoking among ischemic stroke patients with serum homocysteine levels ≤ 15µmol/L was meaningfully less(9.52%) compared to in patients with serum homocysteine levels > 15µmol/L(42.59%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that majority of the smokers are associated with higher serum homocysteine levels > 15µmol/L in ischaemic stroke patients. This also proves

there is an increasing trend of having higher serum homocysteine levels among smokers in our study.

Alcoholism



Alcoholism	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	
Absent	19	90.48	36	66.67
Present	2	9.52	18	33.33
Total	21	100	54	100
Chi-square Statistic		4.38		
Degrees of freedom		1		
P value Chi Squared Test		0.036		

By conventional criteria the association between the serum homocysteine groups and alcoholism is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of alcoholism is 2 in patients with serum homocysteine levels ≤ 15µmol/L and 18 in patients with serum homocysteine levels > 15µmol/L with a p-value of 0.036 according to Chi-Squared test.

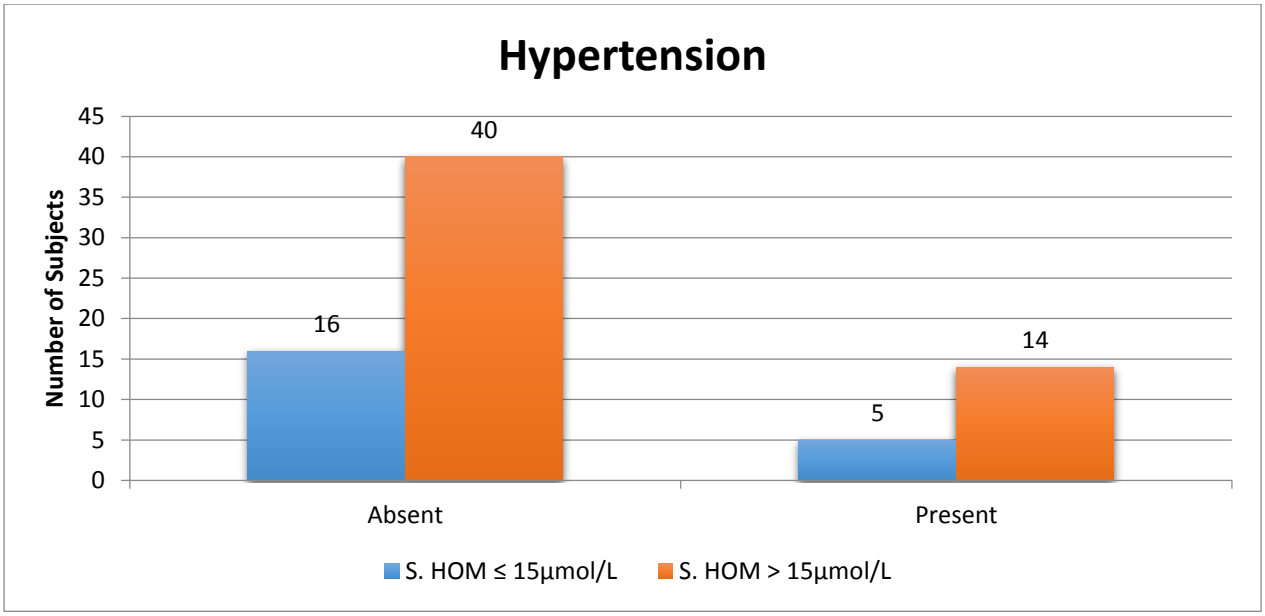
Clinical Significance

The incidence of alcoholism among ischemic stroke patients with serum homocysteine levels ≤ 15µmol/L was meaningfully less(9.52%) compared to in patients with serum homocysteine levels > 15µmol/L(33.33%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that alcoholism in our study is associated with higher serum homocysteine levels > 15µmol/L in ischaemic stroke patients. This also proves there is an increasing trend of having higher serum homocysteine levels among patients suffering from alcoholism in our study.

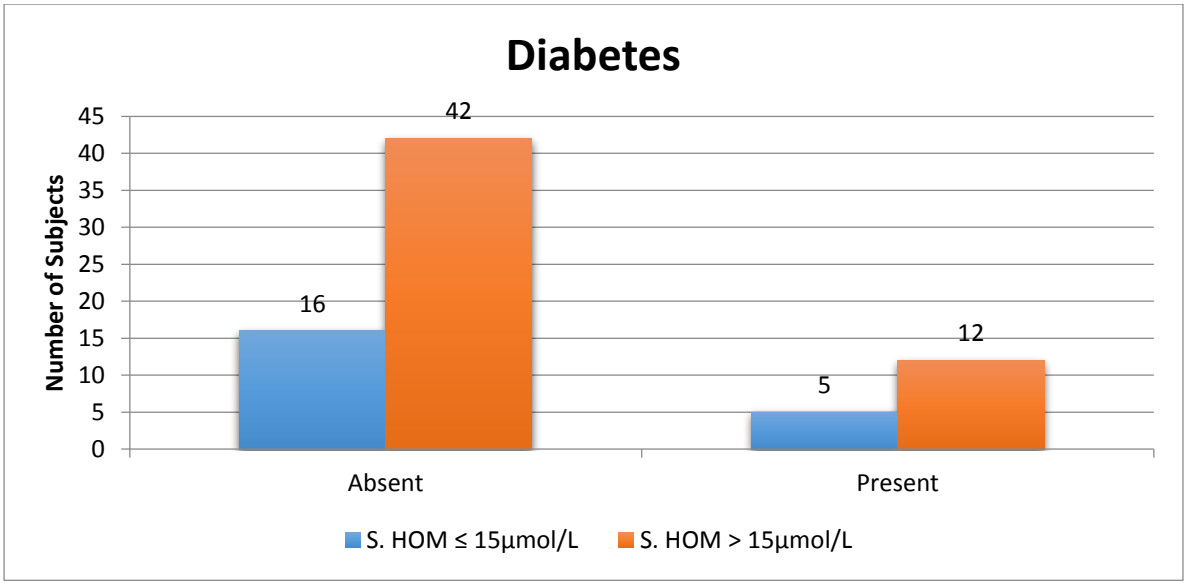
Hypertension



Hypertension	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	
Absent	16	76.19	40	74.07
Present	5	23.81	14	25.93
Total	21	100	54	100
Chi-square Statistic		0.358		
Degrees of freedom		1		
P value Chi Squared Test		0.850		

By conventional criteria the association between the serum homocysteine groups and hypertension is considered to be not statistically significant since $p > 0.05$.

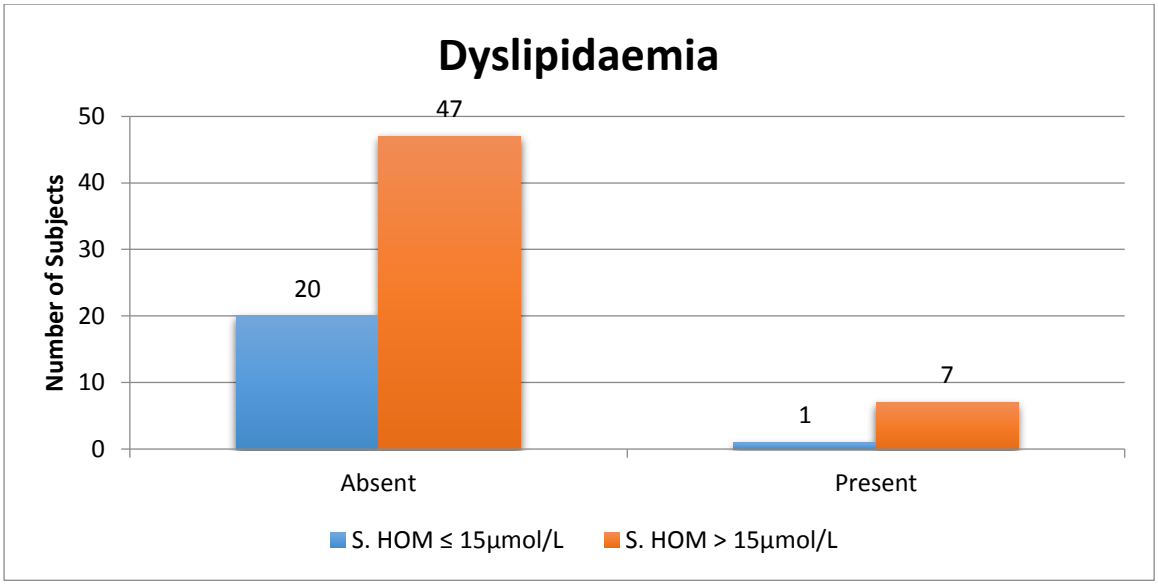
Diabetes



Diabetes	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	
Absent	16	76.19	42	77.78
Present	5	23.81	12	22.22
Total	21	100	54	100
Chi-square Statistic		0.217		
Degrees of freedom		1		
P value Chi Squared Test		0.883		

By conventional criteria the association between the serum homocysteine groups and diabetes mellitus is considered to be not statistically significant since p > 0.05.

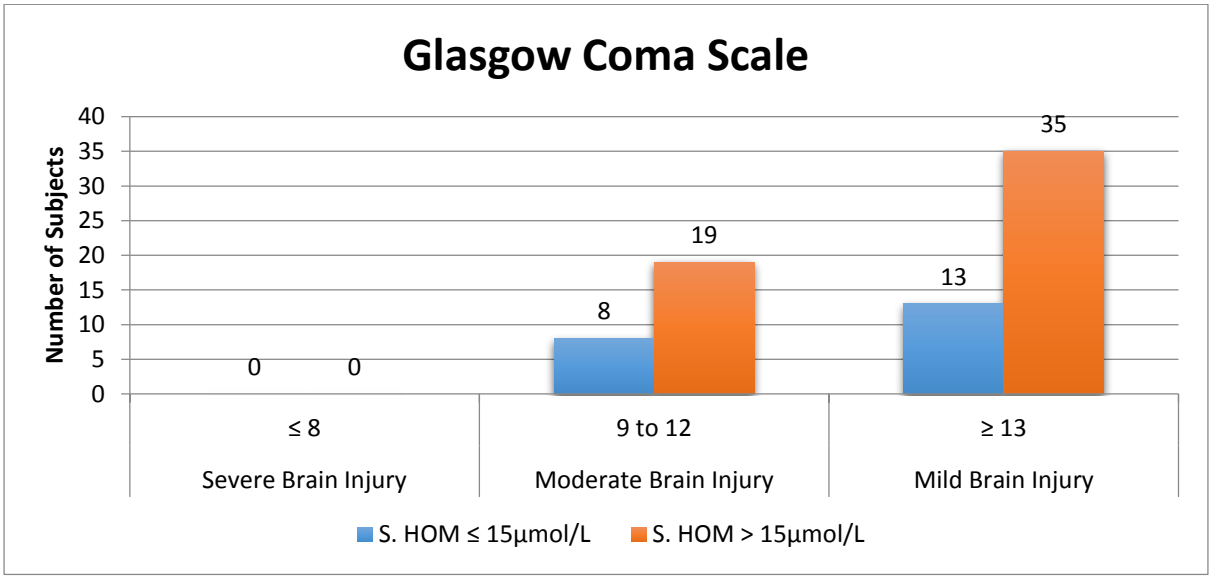
DYSLIPIDEMIA



Dyslipidaemia	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	
Absent	20	95.24	47	87.04
Present	1	4.76	7	12.96
Total	21	100	54	100
Chi-square Statistic		1.07		
Degrees of freedom		1		
P value Chi Squared Test		0.302		

By conventional criteria the association between the serum homocysteine groups and hyperlipidaemia is considered to be not statistically significant since $p > 0.05$.

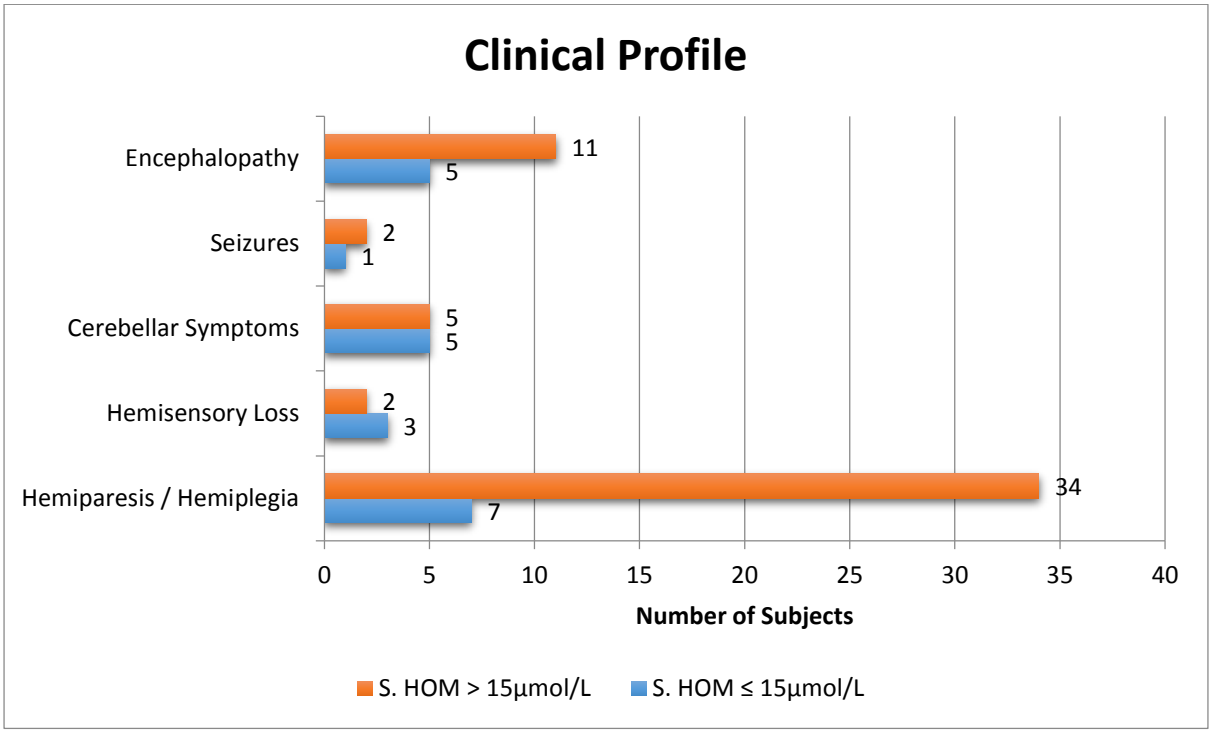
Glasgow Coma Scale



Brain Injury	Glasgow Coma Scale	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%
Severe Brain Injury	≤ 8	0	0.00	0	0.00
Moderate Brain Injury	9 to 12	8	38.10	19	35.19
Mild Brain Injury	≥ 13	13	61.90	35	64.81
Total		21	100	54	100
Chi-square Statistic		0.556			
Degrees of freedom		1			
P value Chi Squared Test		0.814			

By conventional criteria the association between the serum homocysteine groups and Glasgow coma scores are considered to be not statistically significant since $p > 0.05$.

Clinical Profile



Clinical Profile	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%	P value Chi Squared Test
Hemiparesis / Hemiplegia	7	33.33	34	62.96	0.021
Hemisensory Loss	3	14.29	2	3.70	0.099
Cerebellar Symptoms	5	23.81	5	9.26	0.096
Seizures	1	4.76	2	3.70	0.834
Encephalopathy	5	23.81	11	20.37	0.744
Total	21	100	54	100	

By conventional criteria the association between the serum homocysteine groups and clinical features like hemisensory loss, cerebellar symptoms, seizures and encephalopathy are considered to be not statistically significant since $p > 0.05$.

By conventional criteria the association between the serum homocysteine groups and hemiparesis/hemiplegia is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of hemiparesis/hemiplegia is 7 in patients with serum homocysteine levels ≤ 15µmol/L and 34 in patients with serum homocysteine levels > 15µmol/L with a p-value of 0.021 according to Chi-Squared test.

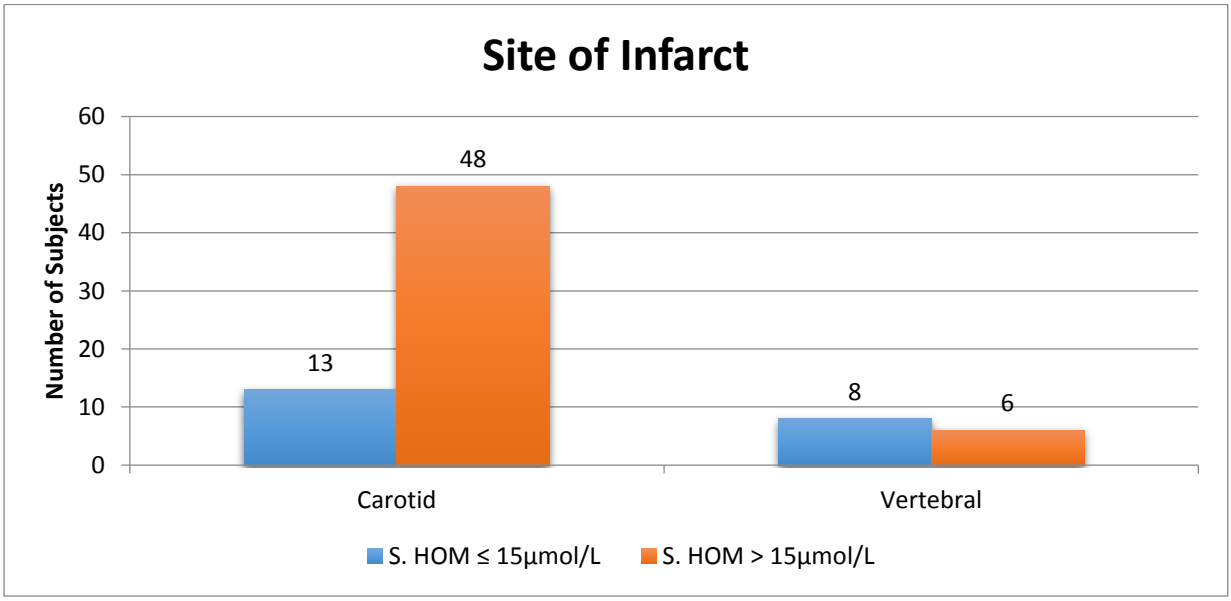
Clinical Significance

The incidence of hemiparesis/hemiplegia among ischemic stroke patients with serum homocysteine levels ≤ 15µmol/L was meaningfully less(17.07%) compared to in patients with serum homocysteine levels > 15µmol/L(82.93%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that hemiparesis/hemiplegia in our study is associated with higher serum homocysteine levels > 15µmol/L in ischaemic stroke patients. This also proves there is an increasing trend of having higher serum homocysteine levels among patients suffering from hemiparesis/hemiplegia in our study.

Site of Infarct



Site of Infarct	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	
Carotid	13	61.90	48	88.89
Vertebral	8	38.10	6	11.11
Total	21	100	54	100
Chi-square Statistic		7.25		
Degrees of freedom		1		

P value Chi Squared Test	0.007

By conventional criteria the association between the serum homocysteine groups and site of infarct is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of infarct in carotid artery is 13 in patients with serum homocysteine levels ≤ 15µmol/L and 48 in patients with serum homocysteine levels > 15µmol/L with a p-value of 0.007 according to Chi-Squared test.

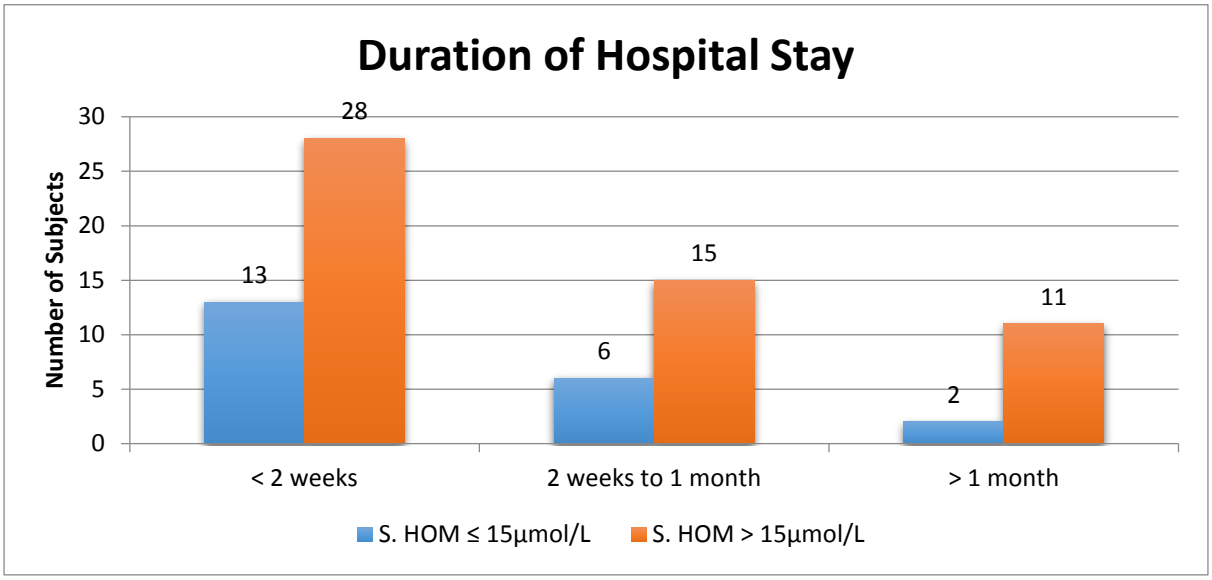
Clinical Significance

The incidence of infarct in carotid artery among ischemic stroke patients with serum homocysteine levels ≤ 15µmol/L was meaningfully less(61.90%) compared to in patients with serum homocysteine levels > 15µmol/L(89.99%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that infarcts in carotid artery in our study is associated with higher serum homocysteine levels > 15µmol/L in ischaemic stroke patients. This also proves there is an increasing trend of having higher serum homocysteine levels among patients suffering from infarct in carotid artery in our study.

Duration of Hospital Stay

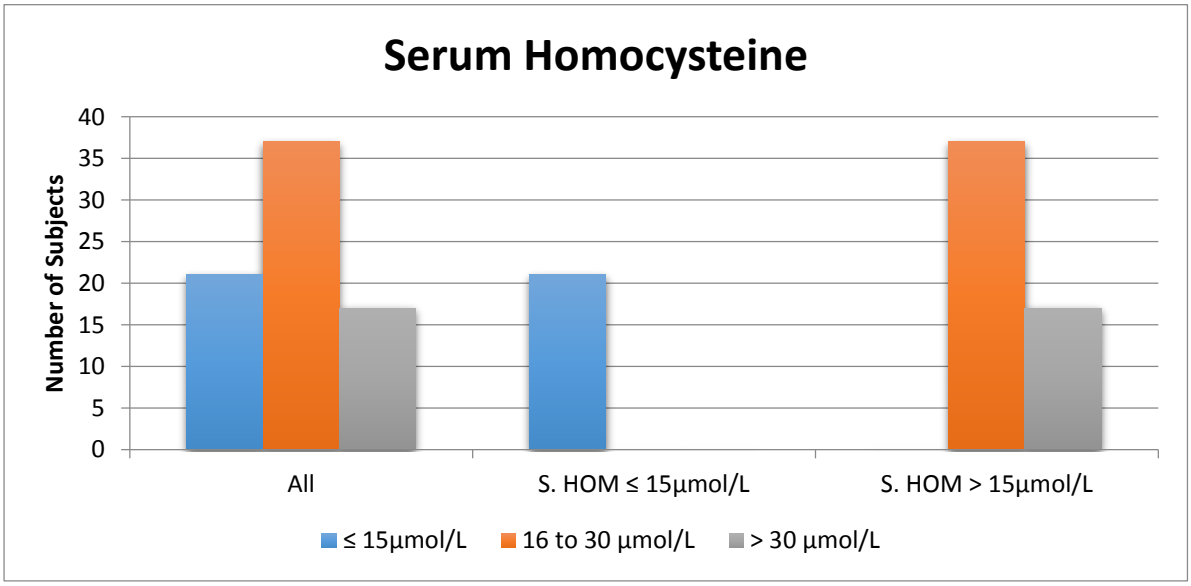


Duration of Hospital Stay	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%
< 2 weeks	13	61.90	28	51.85
2 weeks to 1 month	6	28.57	15	27.78
> 1 month	2	9.52	11	20.37
Total	21	100	54	100
Chi-square Statistic		1.31		
Degrees of freedom		2		

P value Chi Squared Test	0.520

By conventional criteria the association between the serum homocysteine groups and duration of stay in hospital are considered to be not statistically significant since $p > 0.05$.

Serum Homocysteine



Serum Homocysteine	All	%	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%
≤ 15µmol/L	21	28.00	21	100.00	0	0.00
16 to 30 µmol/L	37	49.33	0	0.00	37	68.52
> 30 µmol/L	17	22.67	0	0.00	17	31.48
Total	75	100	21	100	54	100

Serum Homocysteine	All	S. HOM ≤ 15µmol/L	S. HOM > 15µmol/L
N	75	21	54
Mean	24.19	11.99	28.93
SD	12.25	1.71	11.25
P value Unpaired t- test		0.000	

By conventional criteria the association between the serum homocysteine groups is considered to be statistically significant since $p < 0.05$.

Statistical Significance

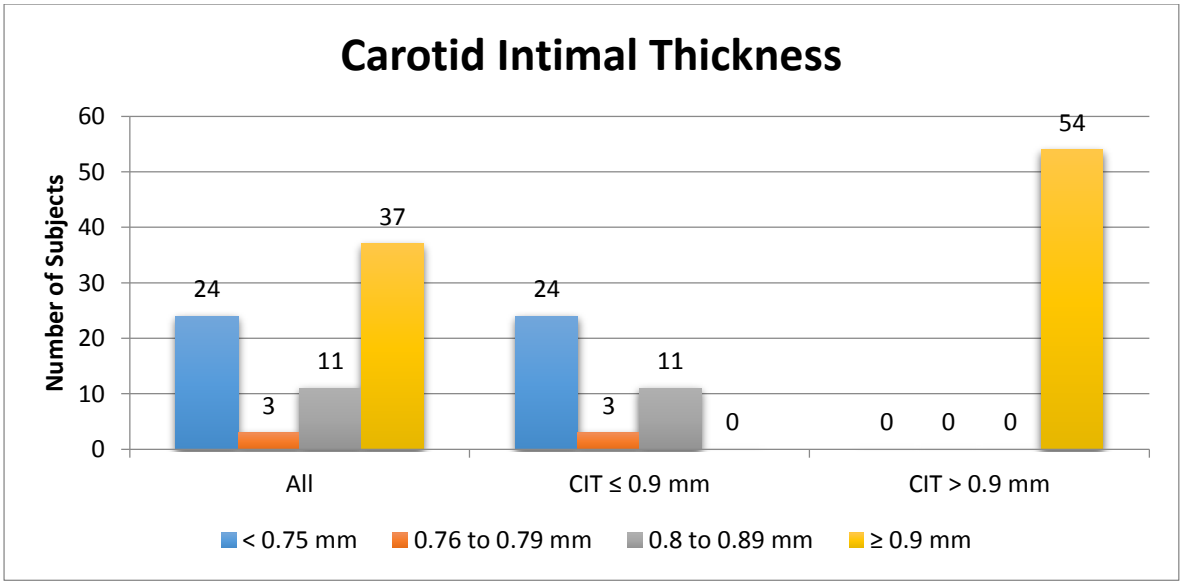
This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the average serum homocysteine values in serum homocysteine levels ≤ 15µmol/L group is 11.99±1.71 µmol/L and in serum homocysteine levels > 15 µmol/L group is 28.93±11.25 µmol/L with a p-value of 0.000 according to Unpaired t test.

Clinical Significance

The average serum homocysteine values among ischemic stroke patients with serum homocysteine levels ≤ 15µmol/L was meaningfully 2.41 times less compared to in patients with serum homocysteine levels > 15µmol/L with a difference of 16.94 µmol/L . This difference is true and significant and has not occurred by chance.

Carotid Intimal Thickness



Carotid Intimal Thickness	All	%	CIT ≤ 0.9 mm	%	CIT > 0.9 mm	%
< 0.75 mm	24	32.00	24	114.29	0	0.00
0.76 to 0.79 mm	3	4.00	3	14.29	0	0.00

0.8 to 0.89 mm	11	14.67	11	52.38	0	0.00
≥ 0.9 mm	37	49.33	0	0.00	54	100.00
Total	75	100	38	180.9524	54	100

Carotid Intimal Thickness	All	CIT ≤ 0.9 mm	CIT > 0.9 mm
N	75	38	54
Mean	24.19	0.71	1.25
SD	12.25	0.08	0.16
P value Unpaired t- test		0.000	

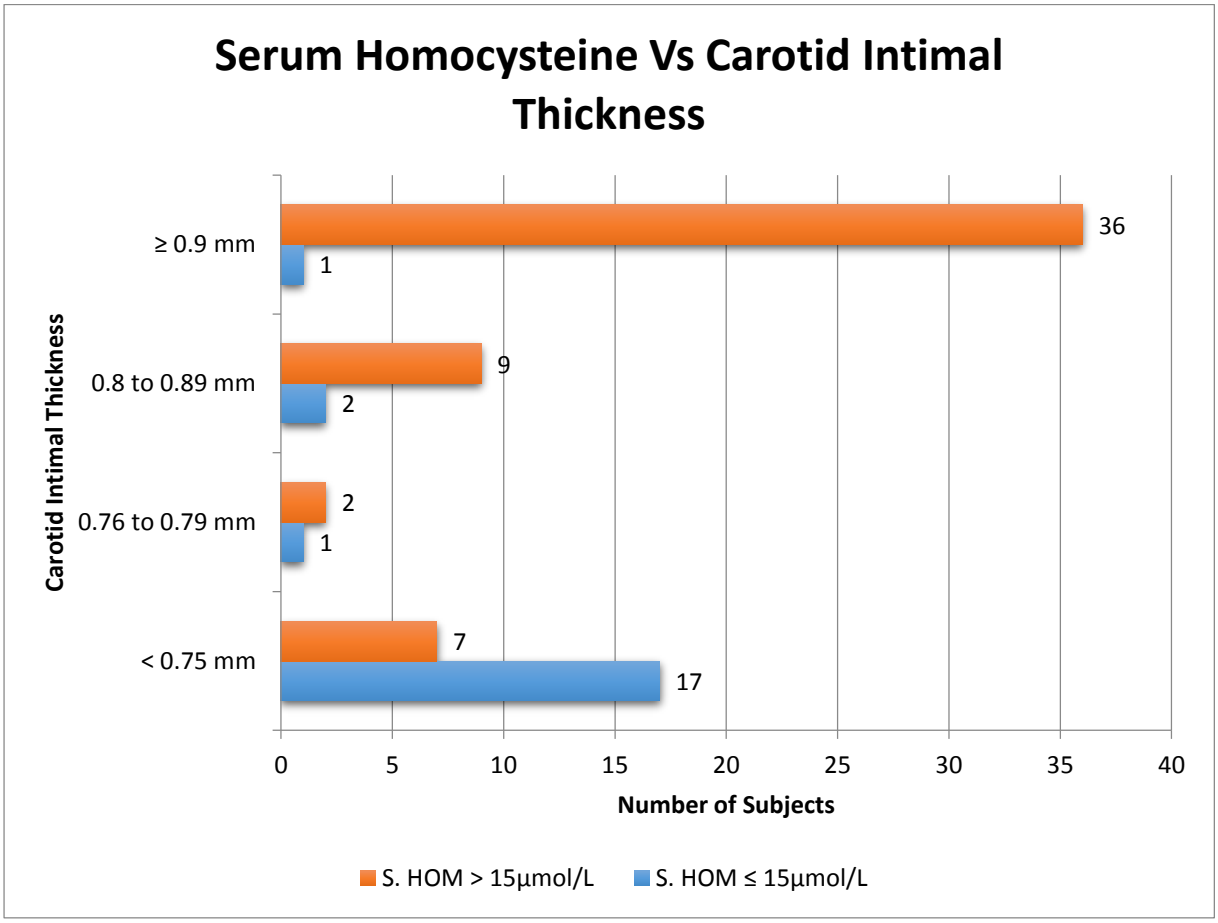
By conventional criteria the association between the carotid intimal thickness groups is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the average carotid intimal thickness values in CIT ≤ 0.9 mm group is 0.71±0.08 mm and in CIT > 0.9 mm group is 1.25±0.16 mm with a p-value of 0.000 according to Unpaired t test.

Serum Homocysteine Vs Carotid Intimal Thickness



Carotid Intimal Thickness	S. HOM ≤ 15µmol/L	%	S. HOM > 15µmol/L	%
< 0.75 mm	17	80.95	7	12.96
0.76 to 0.79 mm	1	4.76	2	3.70
0.8 to 0.89 mm	2	9.52	9	16.67
≥ 0.9 mm	1	4.76	36	66.67
Total	21	100	54	100

Carotid Intimal Thickness	S. HOM ≤ 15µmol/L	S. HOM > 15µmol/L
N	21	54
Mean	0.69	1.05
SD	0.13	0.26
P value Unpaired t- test	0.0000	

Pearson's Correlation	*Serum Homocysteine (µmol/L)*	*Carotid Intimal Thickness (in mm)*
Serum Homocysteine (µmol/L)	1	
Carotid Intimal Thickness (in mm)	-0.798708376	1

By conventional criteria the association between the serum homocysteine groups carotid intimal thickness values are considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the average carotid intimal thickness values in serum homocysteine levels ≤ 15µmol/L group is 0.69±0.13 mm and in serum homocysteine levels >

15 µmol/L group is 1.05±0.26 mm with a p-value of 0.0000 according to Unpaired t test.

There is a strong positive correlation between serum homocysteine levels and carotid intimal thickness measurements. This is indicated by the Pearson's R Correlation value of -0.798708376. This means as serum homocysteine increases the carotid intimal thickness measurement increase in ischaemic stroke patients

Clinical Significance

The average carotid intimal thickness values among ischemic stroke patients with serum homocysteine levels ≤ 15µmol/L was meaningfully less 1.52 times less compared to in patients with serum homocysteine levels > 15µmol/L with a reduction of 0.36 mm . This difference is true and significant and has not occurred by chance.

The increase in carotid intimal thickness measurements in ischemic stroke patients correlates positively, directly and strongly with the serum homocysteine levels. This means that the 66.67% increase in patients with CIT ≥ 0.9 mm in serum homocysteine levels > 15µmol/L group smoking is true 79.87% of times

Similarly in carotid intimal thickness measurements in ischemic stroke patients the 80.95% decrease in patients with CIT < 0.75 mm in serum homocysteine levels ≤ 15µmol/L group smoking is true 79.87% of times

Conclusion

We conclude that in our study the patients with higher carotid intimal thickness are associated with higher serum homocysteine levels (> 15µmol/L) in ischaemic stroke patients. This also proves there is an increasing trend of having higher serum homocysteine levels among patients with higher carotid intimal thickness in our study.

VI. CITATIONS

1. The Northern Manhattan study ,by the department of neurology in Columbia university in New York USA, studied the correlation between homocysteine and ischemic stroke found out that total homocysteine levels more than 15 micromole/l is an independent risk factor for ischemic cerebrovascular diseases. They also found that these effects are more in whites and Hispanics. But homocysteine levels between 10 and 15 micromol/l were less predictive.
2. The Rotterdam study , by Michiel L. Bots et al, studied whether carotid intima medial thickness was associated with an increased future risk of cerebrovascular and cardiovascular diseases, and they concluded at the end of their study that an increased common carotid intima media thickness is associated with future cardiovascular and cerebrovascular events.
3. Venkatasubramanian et al studied the relation between hyperhomocysteinemia and risk of ischemic stroke in young Asian adults , and they also concluded that there is a strong, graded and significant relationship between stroke risk and hyperhomocysteinemia., and the proatherogenic effect of homocysteine is responsible for the increased incidence of stroke in these people.

4. The Atherosclerosis Risk in Communities (ARIC) study, by Chambless et al, also demonstrated hyperhomocysteinemia was associated with an increased risk for thickening of the carotid artery intima media wall.
5. The Perth Carotid Ultrasound Disease Assessment Study (CUDAS) associated carotid intima media thickness with homocysteine levels in asymptomatic patients.
6. Voutilainen et al also found an association between plasma total homocysteine and increased common carotid artery thickness using B-mode USG, in Finnish people.
7. In India, the Ruby Hall study in Pune and another independent study done in Guwahati demonstrated hyperhomocysteinemia in ischemic stroke. The Ruby Hall study estimated serum homocysteine, folate and vit B12 in ischemic stroke patients, and they found ~74 % of arterial strokes had increased homocysteine. The Guwahati study demonstrated ~ 60% patients had hyperhomocysteinemia.
8. Homocysteine and Atherosclerosis Reduction Trial (HART) done in Japan demonstrated an association between elevated homocysteine and increased common carotid media thickness.
9. P Poredos et al demonstrated that carotid intima media thickness is a measure of extent of atherosclerosis and is an indicator for cardiovascular and stroke risk.

10. In the Journal of Hypertension (feb 2002), the importance of carotid intima media thickness was discussed as a new tool for diagnosis and treatment of cardiovascular risk. They noted that increased intima media thickness is a powerful predictor of cardiac and cerebrovascular complications.
11. A case control study done in JIPMER, India , in 2009, regarding common carotid intima media thickness in acute ischemic stroke, found that patients with ischemic stroke had a significantly higher intimal thickness as compared to controls.
12. A recent study published in *Neurology* journal in October 2013 showed a meta-analysis on vitamin B supplementation, homocysteine levels and risk of cerebrovascular diseases, in which 14 RCTs were studied and they concluded that vitamin B supplementation for homocysteine reduction significantly reduced stroke levels.

VII. CONCLUSION

Hyperhomocysteinemia is closely related to ischemic stroke. It has been recognised as a prothrombotic and proatherosclerotic state and is attributed as one of the causes of ischemic stroke.

In my study, the prevalence of hyperhomocysteinemia in patients with ischemic stroke was 54 out of 75 patients ,ie. 72 %. It correlates with various other Indian studies done elsewhere.

It was also found that serum homocysteine levels correlated with alcoholism and smoking as p values were significant (<0.05).

The correlation of homocysteine to age, gender, diabetes, hypertension, dyslipidemia, glasgow coma scale score at time of presentation and the duration of hospital stay was not statistically significant.

The clinical profile of ischemic stroke patients getting admitted in Government Stanley Hospital, Chennai revealed that the most common presentation during admission is a hemiplegia/hemiparesis (41 patients out of 75). Other presentations in decreasing order of frequency include acute encephalopathy followed by cerebellar symptoms, hemisensory loss and seizures.

A statistically significant correlation was found between the serum homocysteine levels and hemiparesis/hemiplegia, and also the site of infarct, as

majority of the anterior circulation strokes involving the carotid artery, was found to have a significantly elevated homocysteine values.

My study also found a statistically significant positive correlation between the serum homocysteine levels and the carotid intima media thickness.

As per previous studies elsewhere as given in the citations, and my study, I conclude that there is a high prevalence of hyperhomocysteinemia in ischemic stroke patients and also the patients with higher carotid intimal thickness are associated with higher serum homocysteine levels (> 15µmol/L) in ischaemic stroke patients.

More studies with similar indices have to be done to confirm the results.

I also conclude that homocysteine measurements and carotid intima media thickness measurements in ischemic stroke patients are warranted.

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CLINICAL PROFILE

NAME	
AGE /SEX:	
OCCUPATION:	
ADDRESS WITH CONTACT NO:	
IP NO/OP NO:	
DATE OF ADMISSION:	
DATE OF DISCHARGE	

MOTOR WEAKNESS		**CHEST PAIN**	
SENSORY DISTURBANCES		**DYSPNEA**	
ALTERED SENSORIUM		**PEDAL EDEMA**	
CRANIAL NERVE DISTURBANCES		**COUGH / HEMOPTYSIS**	
LOSS OF CONSCIOUSNESS		**PALPITATIONS**	
HEADACHE		**SYNCOPE**	
VOMITING		**FEVER**	
SEIZURES		**OLIGURIA**	

PERSONAL H/O :

SMOKER		**ALCOHOLIC**	

PAST H/O :

DIABETES		**EPILEPTIC**	
HYPERTENSION		**DYSLIPIDEMIA**	
CAD		**CVA**	

EXAMINATION :

PALLOR		**CVS**	
ICTERUS		**RS**	
PEDAL EDEMA		**P/A**	
BP		**CNS**	
PR			

CNS EXAMINATION :

HIGHER MENTAL FUNCTIONS :

CRANIAL NERVES :

SPINOMOTOR SYSTEM :

RIGHT LEFT

- **POWER - UPPER LIMBS**

  LOWER LIMBS

- **TONE – UPPER LIMBS**

  LOWER LIMBS

- **BULK – UPPER LIMBS**

  LOWER LIMBS

- **SUPERFICIAL REFLEXES**
- **DEEP TENDON REFLEXES**
- **PLANTAR**
- **GAIT**
- **INVOLUNTARY MOVEMENTS**

SENSORY SYSTEM :

CEREBELLUM :

DORSAL COLUMN :

AUTONOMIC NEERVOUS SYSTEM :

SPINE AND CRANIUM :

SIGNS OF MENINGEAL IRRITATION :

FEATURES OF INCREASED INTRACRANIAL TENSION :

INVESTIGATIONS

Hb	
TC	
DC	
PLATELETS	
ESR	
PCV	
RBS	
UREA	
CREATININE	
Na+	
K+	
Cl-	
TOTAL BILIRUBIN	
DIRECT BILIRUBIN	
PROTEINS	
ALBUMIN	
SGOT	
SGPT	
ALP	

TOTAL CHOLESTEROL	
TRIGLYCERIDES	
HDL	
LDL	
VLDL	
ECG	
ECHOCARDIOGRAM	
CT BRAIN	
SERUM HOMOCYSTEINE	
CAROTID INTIMAL THICKNESS	

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

A STUDY ON HYPERHOMOCYSTEINEMIA IN PATIENTS WITH ISCHEMIC STROKE AND CORRELATION WITH CAROTID INTIMAL THICKNESS OF THESE PATIENTS AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

Place of study: govt. Stanley medical college, Chennai

I ..... have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:

Name and address
Signature/thumb impression:
Date:

Witness:

Name and address
Signature/thumb impression
Date:

Investigator

Signature and date

அரசு. ஸ்டான்லி மருத்துவ கல்லூரி, சென்னை – 600001

A STUDY ON HYPERHOMOCYSTEINEMIA IN PATIENTS WITH ISCHEMIC STROKE AND CORRELATION WITH CAROTID INTIMAL THICKNESS OF THESE PATIENTS AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றி நான் அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்ப முடியும், அதன் பின்னர், நான் வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெற முடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்க கூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்
பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:

சாட்சி
பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:

ஆராய்ச்சியாளராக
கையொப்பம் மற்றும் தேதி

இரத்த நாளங்களின் அடைப்பினால் பக்கவாதம் ஏற்பட்டு அரசாங்க ஸ்டான்லி மருத்துவமனைக்கு வரும் நோயாளிகளின் இரத்த ஹோமோசிஸ்டீன் அளவிற்கும் கரோடிட் இரத்த நாளத்தின் தடிம அளவற்க்கும் உள்ள தொடர்பினை கண்டறிவதற்கான ஒரு ஆய்வு

ஆய்வாளர்:மரு. **அப்புன்னி**,

முதுநிலைபட்டமேற்படிப்புமாணவர்,

பொதுமருத்துவ பட்டபடிப்பு.

வழிகாட்டி : **பேராசிரியர் மரு. சௌந்தராஜன்**

பொதுமருத்துவபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

<u>பங்கேற்பாளரின்தகவல்படிவம்</u>

நீங்கள் இந்த ஆய்வில் பங்கேற்க அழைக்கப்படுகிறீர்கள். இந்த ஆய்வில் பங்கேற்கும்முன், இதன் நோக்கத்தையும், முறைகளையும் ,இதனால் ஏற்படும் பின்விளைவுகளையும் நீங்கள் அறிந்து கொள்ள ஆய்வாளர் அளிக்கும் தகவல்:

உங்கள் நோயின் வரலாறும், உங்களின் முழு உடல்பரிசோதனையும் தெளிவாகவும் விரிவாகவும் பதிவுசெய்யப்படும்.

இந்த ஆய்வின் முடிவுகள் மருத்துவ காரணங்களுக்காகவும், மருத்துவ கல்விக்காகவும் பயன்படுத்தப்படும். இந்த ஆய்வு பற்றிய சந்தேகங்களுக்கு உரிய முறையில் விளக்கமளிக்கப்படும். தங்களைப்பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும்.

இந்த ஆய்வில் இருந்து எப்போது வேண்டுமானாலும் தாங்கள் எவ்வித முன்னறிவிப்பின்றியும், எவ்வித சட்டசிக்கலும் இன்றி விலகிக்கொள்ளலாம்.

இந்த ஆய்வில் பங்கேற்குமாறு கேட்டுக்கொள்கிறேன்.

நன்றி,

ஆய்வாளர் கையொப்பம்

(மரு. **அப்புன்னி**)

நோயாளியின் கையொப்பம்

(பெயர்:)

ETHICAL COMMITTEE APPROVAL LETTER

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study on Hyperhomocysteinemia in ischemic stroke and correlation with carotid intimal thickness of these patients at Govt Stanley Hospital, Chennai

Principal Investigator : Dr. Appunni.S

Designation : PG in MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 01.04.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MASTER CHART

S. NO	AGE	SEX	RISK FACTORS	GCS	CLINICAL PROFILE	CT BRAIN	SERUM HOMOCYSTEINE (µmol/L)	CAROTID INTIMAL THICKNESS (in mm)	DURATION OF HOSPITAL STAY
1	63	M	1, 3	15	A	1	27.3	0.95	A
2	55	F	-	15	A	1	26.9	0.81	A
3	58	M	2	14	E	1	39.3	1.30	B
4	32	M	1	11	E	1	41.1	1.12	C
5	35	F	-	15	A	1	22.0	0.60	A
6	44	M	-	15	B	1	11.3	0.58	A
7	41	M	4	15	C	2	33.5	1.08	A
8	77	F	4	12	E	1	14.0	0.68	B
9	84	M	1,3,4	10	E	1	26.2	1.20	C
10	29	F	-	15	A	1	42.0	1.34	B
11	54	F	4	15	B	1	11.0	0.65	A
12	58	M	1,2	10	E	2	13.4	0.82	C
13	62	M	2,3	14	C	2	44.6	1.40	B
14	30	M	-	15	A	2	75.9	1.42	B
15	42	F	-	15	A	1	11.3	0.62	A
16	75	M	1,2,5	11	E	1	52.7	1.40	C
17	67	F	3	14	C	2	13.0	0.64	A
18	68	M	1,4,5	10	E	1	57.3	1.42	C
19	55	F	3,4,5	15	A	1	41.2	1.20	A
20	43	F	-	15	A	1	27.3	0.72	A
21	51	M	-	15	A	1	22.2	0.70	A
22	54	M	1	14	A	1	29.2	0.80	A
23	53	F	-	15	B	1	13.0	0.64	A
24	41	F	5	15	A	1	19.3	0.70	A
25	55	M	1	13	A	1	11.1	0.62	A
26	71	M	3,4,5	9	E	1	13.9	1.20	C
27	80	F	3	11	E	2	10.3	0.68	B
28	29	M	2	15	A	1	8.3	0.62	A
29	40	M	1,2	14	A	1	33.8	1.20	A
30	70	M	3	12	D	1	31.7	1.16	B
31	65	F	-	15	A	2	12.2	0.62	A
32	52	M	-	15	A	1	31.1	1.00	A
33	41	M	1	14	C	2	21.0	0.82	A
34	45	F	-	13	A	1	23.3	0.84	B
35	54	M	3	13	A	1	17.2	0.68	B

36	53	M	-	15	A	1	15.5	0.64	A
37	86	M	3,5	11	E	1	29.2	1.32	C
38	27	F	-	15	A	1	31.1	1.20	A
39	39	M	-	13	A	1	27.3	1.15	B
40	62	F	-	15	C	2	22.2	0.78	A
41	71	F	-	14	B	1	18.3	0.80	A
42	80	M	2	10	E	1	27.6	1.22	C
43	33	M	1	14	A	1	22.4	1.02	A
44	57	F	-	11	D	1	12.9	0.80	B
45	63	M	1,2	14	A	1	22.3	0.82	A
46	30	M	1,2	11	A	1	18.2	0.80	B
47	49	M	-	10	C	2	13.3	0.70	B
48	70	M	2	11	A	1	30.0	1.40	B
49	74	F	4	9	E	1	21.1	1.24	C
50	60	M	3,4,5	10	A	1	22.1	1.26	C
51	62	F	4	15	A	1	13.9	0.64	A
52	42	F	3,4	14	C	2	16.2	0.66	A
53	39	M	1,2	11	A	1	39.3	1.44	C
54	77	M	1,2	12	A	1	33.2	1.32	B
55	43	F	3	14	C	2	11.2	0.62	A
56	88	M	3,4,5	9	E	1	19.9	1.00	B
57	60	M	1	15	A	1	21.3	0.80	A
58	52	F	-	14	C	2	8.1	0.64	A
59	61	M	1	14	A	1	29.1	1.12	A
60	45	M	1,2	15	A	1	25.1	1.08	A
61	50	M	-	11	E	1	13.8	0.66	B
62	38	M	1,2	10	A	1	39.1	1.52	C
63	82	F	3,4	12	A	1	18.2	0.92	B
64	75	M	1,2,3	14	A	1	24.2	0.96	A
65	40	M	1,2	14	A	1	25.8	1.02	A
66	51	F	-	15	C	2	11.2	0.64	A
67	71	M	2,4	14	B	1	18.2	0.76	A
68	56	F	3	10	E	1	16.3	0.80	B
69	70	M	1,2,4	9	E	1	28.2	1.44	C
70	29	F	-	15	A	1	11.4	0.62	A
71	81	F	3,4	12	A	1	13.2	0.78	B
72	40	M	1,2	15	A	1	29.1	1.12	A
73	70	F	-	10	D	1	19.2	1.00	B
74	65	M	1,2,3	14	A	1	27.7	1.10	A
75	72	M	1,2	15	A	1	38.6	1.28	A

ABBREVIATIONS :

SEX :

M – MALE

F – FEMALE

RISK FACTORS :

1 – SMOKING

2 – ALCOHOLISM

3 – HYPERTENSION

4 – DIABETES MELLITUS

5 – DYSLIPIDEMIA

GCS – GLASGOW COMA SCALE

Maximum score = 15

Minimum score = 3

Glasgow Coma Scale

Best eye response (E)	Spontaneous--open with blinking at baseline	4
	Opens to verbal command, speech, or shout	3
	Opens to pain, not applied to face	2
	None	1
Best verbal response (V)	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best motor response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1

CLINICAL PROFILE :

A – HEMIPARESIS / HEMIPLEGIA

B – HEMISENSORY LOSS

C – CEREBELLAR SYMPTOMS

D – SEIZURES

E - ENCEPHALOPATHY

CT BRAIN :

1 – INFARCT IN ANTERIOR CIRCULATION (CAROTID)

2 – INFARCT IN POSTERIOR CIRCULATION (VERTEBRAL)

DURATION OF HOSPITAL STAY :

A – LESS THAN 2 WEEKS

B – 2 WEEKS TO 1 MONTH

C – MORE THAN 1 MONTH